THE

American Journal of Physiology

VOL XXXIII MARCH 2, 1914 NO. III

ON THE PERCENTILE MEASUREMENT OF THE VASOMOTOR REFLEXES

By W. T. PORTER

[*From the Laboratory of Comparative Physiology in the Harvard Medical School*]

PRIOR to 1907 when an afferent vasomotor nerve, for example the sciatic, was stimulated, the resultant change in blood pressure was measured by the extent to which the blood pressure rose above the level at which it stood just before stimulation. This may be called the absolute change in blood pressure. In 1907 it was proposed [1] that the criterion be not the absolute but the percentile change, i.e., that the observed rise or fall be divided by the blood pressure at the beginning of stimulation.

A correct choice between the absolute and the percentile method of reckoning is of the highest importance, because this choice determines quantitatively the normal reflex and such a reflex is the only evidence that the vasomotor apparatus is normal.

The present communication will demonstrate that when the initial blood pressure stands between about 20 and about 90 mm. Hg and the vasomotor nerves are stimulated, the resultant changes in the blood pressure must be measured by the percentile and not the absolute value. Under these conditions, only the percentile value will enable the observer to form correct conclusions regarding the state of the vasomotor apparatus.

The data to be presented are from experiments on cats and rabbits performed from Nov. 6, 1906 to April 4, 1907, and from Sept. 28 to Oct. 23, 1907. The experiments of the first period

[1] W. T. PORTER. This journal, 1907, xx, p. 402; also 1908, xxi, p. 461, and xxiii, p. 132.

were made to determine the effect of hemorrhage on the vasomotor reflexes; those of the second period were part of a study of the vasomotor reflexes in animals of different species; neither investigation was concerned with the problem now in hand.

The blood pressure in these experiments varied naturally or was made to vary by withdrawing small amounts of blood. These amounts were often defibrinated and replaced by injection through the external jugular vein. None of the data used in this paper were taken from animals in which loss of blood had weakened the vasomotor centre. The intervals during which the blood pressure was experimentally lowered were much too short to affect the nutrition of the vasomotor cells. That the vasomotor apparatus actually remained in its usual state was shown by restoring the blood pressure to its usual level and obtaining then the usual (absolute) reflex upon stimulating the sciatic, the brachial, and the depressor nerves.

It being established that the vasomotor arc was normal, it follows that only the reflex that showed this normal state can be correct, and that a reflex indicating an abnormal condition of the vasomotor arc must be misleading.

The result [1] of this enquiry is shown in Table I. It is seen that when the afferent nerves were stimulated at initial pressures varying from 90 to 20 mm. Hg, the absolute resultant change in pressure sank steadily, from which we should be obliged to conclude that the vasomotor arc became progressively incompetent. But the percentile reflex remained almost unaltered. Since it was known that the vasomotor arc remained at its normal level of efficiency, it is obvious that between the initial pressures 90 to 20 mm. Hg [2] the percentile method of measuring the reflex is correct and the absolute method incorrect.

[1] The individual measurements are given in Tables II and III.

[2] At levels above 90 mm. the arteries are so distended that the percentile reflex diminishes. At these high levels the state of the vasomotor cells can probably be determined with the aid of a curve to be constructed from a great number of measurements. It should be observed that in practice the state of the vasomotor centre is seldom a matter of concern when the blood pressure is high. It is precisely when the blood pressure is at the levels measured in this present investigation, as for example in "shock," that correct conclusions regarding the vasomotor arc become essential.

TABLE I

THE PERCENTILE CONTRASTED WITH THE ABSOLUTE CHANGE IN BLOOD PRESSURE ON STIMULATING THE SCIATIC, BRACHIAL, AND DEPRESSOR NERVES.

Nerve	Initial Pressure	Percentile Change	Absolute Change
	Mm. Hg	Per Cent	Mm. Hg
Sciatic	70 to 89 mm. Hg.	73	53
	50–69	74	48
	30–49	70	25
	20–29	73	18
Brachial	70 to 89	69	51
	50–69	68	40
	30–49	67	26
	20–29	64	12
Depressor	70 to 89	36	27
	50–69	32	17
	30–49	30	10
	20–29	—[1]	—[1]

[1] Omitted for lack of a sufficient number of observations.

TABLE II

THE ABSOLUTE CHANGE IN BLOOD PRESSURE ON STIMULATING THE SCIATIC, BRACHIAL, AND DEPRESSOR NERVES.

20 to 29 mm.			30 to 49 mm.			50 to 69 mm.			70 to 89 mm.		
Sc.	Br.	Dpr.	Sc.	Br.	Dpr.	Sc.	Br.	Dpr.	Sc.	Br.	Dpr.
25	20		25	30	13	15	43	25	30	70	35
20	18		30	30	10	40	60	20	74	48	30
21	20		13	30	8	46	30	15	60	40	30
21	6		65	30	7	65	30	21	40	52	15
21	8		10	20	12	62	26	10	25	54	24
22	14		25	25	13	51	44	20	40	44	30
10	13		20	35		66	35	12	52	40	14
8	14		25	15		58	38	16	58	58	14
	12		42	15		30	56		38		20
	5		20	20			30		58		24
	5		45	34			45		65		30
			20	9			40		76		24
			20	23			64		51		48
			18	15			26		80		36
			9	35			32				
			11	42			36				
			25	28							
			49	26							
			32								
			43								
			33								
			8								
			9								
			40								
			7								
			12								
18	12	—	25	26	10	48	40	17	53	51	27
Averages											

TABLE III

THE PERCENTILE CHANGE IN BLOOD PRESSURE ON STIMULATING THE SCIATIC, BRACHIAL, AND DEPRESSOR NERVES.

20 to 29 mm.			30 to 49 mm.			50 to 69 mm.			70 to 89 mm.		
Sc.	Br.	Dpr.	Sc.	Br.	Dpr.	Sc.	Br.	Dpr.	Sc.	Br.	Dpr.
%	%	%	%	%	%	%	%	%	%	%	%
95	100		56	75	34	50	78	45	100	100	47
43	90		100	75	33	23	100	33	75	69	38
100	100		43	100	25	67	50	30	50	48	38
100	30		144	100	23	94	60	36	36	69	35
84	29		33	67	30	130	43	17	57	78	30
84	70		71	63	33	97	70	40	70	59	53
84	65		50	78		93	70	24	67	48	20
37	64		26	45		66	62	27	54	82	22
31	71		55	50		94	93		77		28
	50		93	50		30	54		87		31
	36		50	56			75		67		39
			100	27			69		107		30
			50	75			110		70		54
			50	48			48		100		43
			53	78			50				
			25	100			53				
			53	58							
			104	54							
			100								
			134								
			89								
73	64	—	70	67	30	74	68	32	73	69	36
Averages											

FURTHER OBSERVATIONS ON THE RATE AT WHICH SUGAR DISAPPEARS FROM THE BLOOD OF EVISCERATED ANIMALS

By J. J. R. MACLEOD and R. G. PEARCE

[From the Physiological Department of Western Reserve University]

SINCE the publication, some months ago, of a series of observations bearing on the rate at which sugar disappears from the blood of normal and diabetic dogs after removal of the abdominal viscera, several sources of error that might possibly have interfered with the accuracy of the results have presented themselves. In the present communication are offered the results of further experiments of a similar nature, but in which precautions were taken to avoid these errors.

Although the main conclusion drawn from the previous series of experiments, namely, that there is no appreciable difference in the rate with which sugar disappears from the blood in diabetic as compared with normal animals, has since been confirmed by Patterson and Starling[1] for perfused heart-lung preparations, yet we have thought it advisable to place on record our later results if for no other reason than to show that even when the diabetic state has persisted for over a week, there is no evidence of depressed glycolytic power in eviscerated animals. This conclusion is at variance with the assertion of Verzar[2] that sugar injections do not cause an increase in the respiratory quotient in dogs from whom the pancreas has been removed for more than four days, although such injections do cause a marked increase in the quotient in normal animals.

In the present series of observations the following extra pre-

[1] Patterson, S. W. and Starling, E. H.: Journal of physiology, 1913, xlvii, p. 137.

[2] Verzar, F. and Fejer, A. V.: Biochemische Zeitschrift, 1913, liii, p. 141.

cautions have been taken in performing the evisceration experiments:

1. Using decerebrated animals so that all chances of interference with glycolysis on account of the presence of anaesthetics in the blood might be avoided.

2. Making observations on the percentage of haemoglobin in the blood so as to ascertain to what extent this might be undergoing dilution on account of absorption of fluid from the tissues.

Adopting these precautions, a series of observations was first of all made on several normal animals in the hope that more constant results than those previously published might be secured, with which could be compared not only the glycolysis occurring in diabetic animals, but also that occurring after the administration of adrenalin in normal animals. As the table depicting the results of five such experiments shows, the glycolysis expressed as milligrams of dextrose disappearing from 100 gr. blood per minute varied from 0.47 to 1.8. In no case could more than a small proportion of this disappearance be attributed to dilution of the blood by tissue fluid, this being shown in the sixth column where the percentile dilution of the blood is computed from (1) Hb, (2) decrease in sugar percentage.

With such irregularity in the results, it is obvious that only the most extreme degrees of change in the glycolytic power could be expected to reveal themselves. Any further attempt to investigate the possible influence of adrenalin on the glycolysis was therefore abandoned.

Two experiments were, however, conducted on dogs from which the pancreas had been completely removed eight days previously. The animals were fed on moderate amounts of flesh and gave D : N ratios indicating a marked degree of diabetes. During the evisceration experiments on these diabetic dogs it was necessary to give some adrenalin because the animals were in a depressed condition and it was impossible otherwise to maintain an adequate blood pressure. The results show a more marked degree of glycolysis than normal, which is very probably due to the stimulating influence of the adrenalin on the activity of the heart.

The irregularities in rate of glycolysis which we have found

TABLE I

SUGAR CONSUMPTION IN NORMAL AND DIABETIC EVISCERATED AND DECEREBRATED DOGS

Normal Dogs

No. of expt. / Weight	Time after evisceration (minutes)	Percent dextrose in blood	Mg. dextrose disappearing from 100 gr. blood per min.	Percent Hb	Percent increase in vol. of blood as calculated from: (1) sugar, (2) Hb	Remarks
(1)	(2)	(3)	(4)	(5)	(6)	(7)
I	Immediately	0.066				Starved. Spec. grav. of blood constant. Decerebrate rigidity. B. P. well maintained
	20	0.063				
17 Kg.	40	0.045	0.9			
	60	0.035	0.47			
	80	0.013	1.12			
III	17	0.132		90	Sugar 37	[1] B. P. very low. Rigidity not marked
	37	0.096	1.8	83	Hb 8	
15 Kg.	57	0.083 [1]	0.6			
IV	6	0.209		90	Sugar 23	
13 Kg.	33	0.170	1.4	86	Hb 5	
V	Immediately	0.129		84	Sugar 116	
	20	0.078			Hb 16	
7.9 Kg.	40	0.060	0.91	72		
VII	Immediately	0.257		100	Sugar 29	Adrenalin injected after 20 minutes
	20	0.222	1.75	84	Hb 18	
11.4 Kg.	42	0.199	1.04	86		
	62	(0.203)	—	—		

TABLE I (*continued*)

Diabetic Dogs

No. of expt.	Time after evisceration (minutes)	Percent dextrose in blood	Mg. dextrose disappearing from 100 gr. blood per min.	Percent Hb	Percent increase in vol. of blood as calculated from: (1) sugar, (2) Hb	Remarks
(1)	(2)	(3)	(4)	(5)	(6)	(7)
VIII	Immediately	0.296				8 days after pancreatectomy D:N ratio 2.0 adrenalin
	25	0.212	3.36			
IX	Immediately	0.265		100		8 days after pancreatectomy D:N ratio 2.7. Decerebrate rigidity. Adrenalin
	30	0.207	1.9	92	Sugar 28 Hb 8	
	55	0.140	2.68	84	Sugar 47 Hb 8	

are probably dependent upon irregular consumption by the muscles of the glycogen which is stored within them. In the diabetic animal, as Cruickshank[1] has recently shown, the source of this glycogen may be partly the heart itself. We believe that these irregularities in sugar consumption, not only in our experiments, but also in those on the perfused heart-lung preparation, make it impossible by such methods to arrive at any conclusions as to whether dextrose is any less easily burnt in diabetic as compared with normal animals. Experiments in which the behavior of the respiratory exchange is observed, such as those recorded by Murlin[2] are of much greater value.

[1] CRUICKSHANK: Journal of physiology, 1913, xlvii, p. 1.

[2] MURLIN: The journal of biological chemistry, 1913, xv, p. 365.

SOME FACTORS CONTROLLING THE SHAPE OF THE PRESSURE CURVE IN THE RIGHT VENTRICLE[1]

By CARL J. WIGGERS

[*Department of Physiology, Cornell University Medical College, New York City*]

I. Previous Work

THE controversy as to the correct shape of the intraventricular pressure curve is too well known to demand again an extensive review of the older literature.[2] Briefly recalled, opinions differed as to whether the steep systolic ascent is followed by a flat plateau or a rounded top imperceptibly merging into the descending limb.

So complex and rapid are the pressure changes and consequently so great become the requirements of manometers for their accurate registration that a final direct analysis seemed to some impossible in the rapidly beating mammalian heart. Accordingly, Frank[3] in 1895 sought to approach the subject by studying the isotonic and isometric contraction curves of the frog's heart and the afterloaded curves which resulted when the heart was placed in connection with an artificial circulation scheme. Since the conclusions are of importance in analyzing records obtained from mammals, they may be briefly recalled. Frank found that the height of the isometric pressure curve (obtained by preventing both ventricular outflow and inflow during systole) and, to a certain limit also, the steepness of its ascent increased directly with the initial tension, i.e., the degree of diastolic filling. On

[1] The third of a series of studies on the pulmonary circulation, the previous papers of which were published in this journal, 1912, xxx, p. 233, and 1914, xxxiii, p. 1.

[2] For excellent reviews of the literature see Hill; Schäfer's textbook of physiology, 1900, ii, 18; Tigerstedt: Skandinavisches Archiv für Physiologie, 1912, xxviii, p. 36.

[3] Frank: Zeitschrift für Biologie, 1895, xxxii, p. 370.

the other hand, the height of the isotonic curve, which is proportional to the discharge, decreased with an increase in load. In the afterloaded curve obtained by allowing the heart to eject blood into an artificial system composed of glass tubes but containing also a controllable elastic factor, three phases are recognizable, namely, (1) the period of rising tension (Anspannungszeit), (2) the period of ejection, and (3) the period of relaxation. In the first period, terminating with the opening of the semilunar valves, the curve obeys the law of isometric contraction as far as the incline of its rise is concerned, but its height is modified by the height of the aortic pressure as well as by the initial intraventricular pressure. During the second period the curve rises less rapidly, reaches a summit, and, when the rate of arterial inflow is exceeded by the outflow, the pressure begins to descend in a manner corresponding with that in the aorta, with which the ventricle now forms a common cavity. To this portion of the record, consisting of ascending and descending limbs, the term "plateau," could be applied, but Frank discourages such a terminology since the untenable idea has come to be associated with it, that the pressure remains parallel to the abscissae during this interval.

Such hemodynamic experiments can only be used to forecast the nature of the mammalian intraventricular pressure curve provided it is assumed with Frank that the frog's ventricle beats after the fashion of mammalian hearts. In view of the complicated arrangement of the cardiac musculature in mammals,[1] however, some physiologists would not assent to such an assumption. Consequently, it is desirable to institute mammalian experiments with manometers capable of accurately following the pressure changes within the heart cavities.

By formulating the fundamental guiding principles in manometer construction, Frank[2] has also contributed the essential means for a direct solution of the problem. Thus Straub,[3] Piper,[4] and Tigerstedt[5] all used optically recording instruments of high

[1] MALL: The American journal of anatomy, 1911, ii, p. 211.
[2] FRANK: Zeitschrift für Biologie, 1903, xliv, p. 445.
[3] STRAUB: Archiv für die gesammte Physiologie, 1911, cxliii, p. 69.
[4] PIPER: Archiv für Physiologie, 1912, p. 343.
[5] Skandinavisches Archiv für Physiologie, 1912, xxviii, p. 36.

vibration frequency, whose construction was made possible on the basis of Frank's analysis alone.

Records so obtained have, however, already received different interpretations. Thus Straub described the intraventricular pressure curve as an exceedingly simple curve, evenly rounded at its top and free from sharp secondary vibrations. Piper, on the other hand, described his curves as displaying a rapid rise topped by a few short vibrations and followed by a broadly rounded plateau terminating in an uneventful fall. C. Tigerstedt corroborated the findings of Piper in the left ventricle. His curve, in addition to the superposed vibration at the beginning of the ejection period, gave evidence of a sharp change in the descending limb due to closure of the aortic valves. The top, according to this investigator, may be described as a plateau which is ascending, horizontal, or descending in accordance with the resistance ahead.

In a preliminary communication, the writer[1] pointed out that all optically recorded curves contained certain features in common, but that the general appearance of the records was determined largely by the sensitiveness and damping of the manometer and the speed of the bromide surface. A more careful analysis of a larger number of records shows that other factors may be introduced which account for variations in contour. These were accordingly studied and make the basis of this report.

II. Apparatus and Technic

In order to record the pressure curve within the right ventricle correctly it is necessary to employ a manometer of high vibration frequency, and in order to obtain correct quantitative curves it is important to keep the cannula free from a coagulum and to keep the instrument approximately aperiodic for the pressure changes involved. A new manometer meeting the demands both of accuracy and convenience was therefore devised.

It consists (Figs. 1 and 2) of a vertical glass tube (*A*) surmounted by a hollow brass cylinder (*B*). This contains a stop-

[1] Wiggers: Proceedings of the society for experimental biology and medicine, 1913, xi, p. 11.

cock (*C*) with a conical lumen, the truncated cone of which comes into apposition with a damping plate (*a*) having an opening 2 mm. in diameter. By giving the stopcock a slight turn the instrument can be rendered almost aperiodic to suit any membrane or any pressure change by increasing the damping practically at one point. Above the damping plate the cylinder ends in a segment capsule (*b*) (3 mm. in diameter) covered with rubber dam. Upon

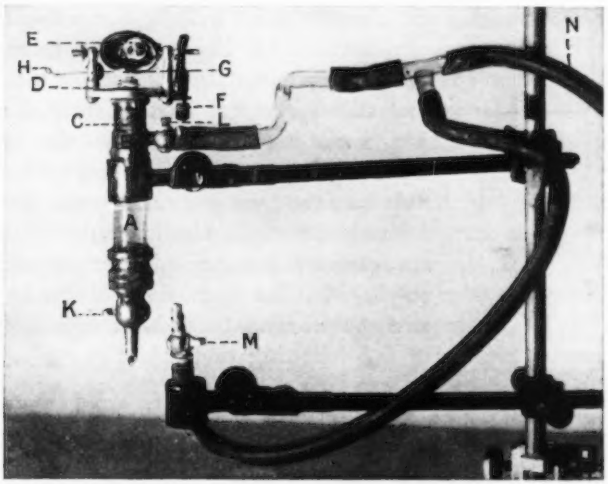


FIGURE 1. Optical manometer, letters referred to in text.

this a small piece of celluloid carrying a little Zeiss mirror (2 x 4 mm.) (*c*) is fastened so that it pivots on the chord side of the segment capsule. Over the segment capsule and its recording mirror is mounted a support (*D*) bearing an inclined reflecting mirror (*E*) adjustable about an horizontal axis by a screw (*F*) so that the image of the recording mirror appears within it. Upon this image the band of light from a Nernst or an arc light is focused. The incident rays are doubly reflected as shown in the diagram of Fig. 2.

For quantitative work the instrument is calibrated with reference to a streak of light projected by a second small mirror (*G*) fastened to one arm of the support and adjusted to the side

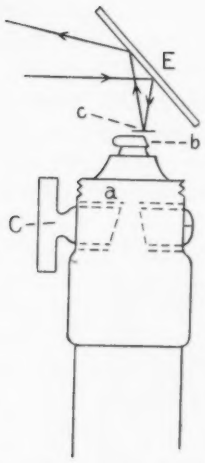


FIGURE 2. Diagram of optical manometer showing internal structure and light reflection. Letters referred to in text.

slightly above the recording mirror, so that it divides the light with the movable mirror and reflects it along a similar path. The distance between the two bands of light thus projected over one another on the recording camera can be adjusted by rotating the small rod (*H*) supporting the calibrating mirror.[1]

The lower end of the manometer is fitted by a conical joint with one of several styles of cannulas. For direct insertion through the ventricular musculature the straight, pointed, and slightly conical cannula (*K*) shown in Fig. 1 was used. For introduction through the auricular appendage a short curved cannula guarded by a stopcock having the same lumen was used, and for introduction through the external jugular a longer cannula was employed. The dimensions of the cannulas and the vibration periods of each are given in the following table.

Type of cannula	Lumen mm.	Length cm.	Vibration rate per second .3 mm.[1]	.43 mm.[1]	1 mm.[1]	Calibration
Straight	4	3.4	100	114	157	2.2[2]
Short curved	3	7.3	50	71	83	1.9[2]
Long curved.....	3.5	12.3	50	66	71	1.1[2]

[1] Figures refer to thickness of membrane.
[2] Figures in column indicate the number of mm. in record equal to 1 mm. pressure change.

In calibrating the instrument, stopcock *K* is closed and stopcock *L* opened. By opening stopcock *M* and placing its outlet on a level with the opening of cannula *K*, the zero level is obtained at any time during an experiment. By closing stopcock *M* and introducing pressure through the tube *N*, communicating with a mercury manometer and pressure flask, one can obtain

[1] It should be stated in justice to the Munich laboratory of physiology, that although the details of construction differ essentially, the convenient principle of light reflection was taken from a manometer in use in Frank's laboratory in 1912 but not yet described.

any series of calibrations in relation to the fixed line given by the second small mirror (*H*).

The cannula is kept free from clots by introducing a few cubic centimetres of anti-coagulating fluid occasionally. The mean pressure may also be read at any time by closing stopcock *N* and opening stopcock *M*.

The technic of insertion is very simple. A direct introduction of the short straight cannula through the right ventricular wall is the procedure of choice, for in this way a normal valve action and a normal transmission of auricular pressure to the ventricle are insured. In this procedure the manometer does not interfere with cardiac movement or contraction, nor, on the other hand, does the cardiac movement jar the instrument materially if a point is selected for insertion where the heart muscle is affected neither by the descent of the base nor the rise of the apex. A window is cut in the pericardium over the area to be utilized. With sharp, pointed scissors a stab is made into the ventricular cavity and the cannula introduced before more than a single spurt of blood takes place. No leakage occurs around the conical cannula, for, aside from its close fit, the intraventricular pressure is very low during diastole and the fibres firmly contracted around the cannula during systole. The entire manometer is then rigidly clamped so as to be, itself, immovable.

The short curved cannula is inserted through the ear of the auricle when it is desired to apply a cardiometer simultaneously to the ventricle, and the long cannula is used only in experiments where it is desired to study the pressure changes in the closed chest.

Right auricular pressure was, as a rule, read by a water manometer introduced through the jugular vein. Carotid or pulmonary arterial pressures were simultaneously recorded in selected experiments.

III. Types of Intraventricular Pressure Curves and their Determining Factors

The Normal Curve. — An intraventricular pressure curve, obtained when right auricular pressure and pulmonary arterial

pressure are approximately those found in naturally breathing animals, may be regarded as a *normal type* in open chest experiments. An "effective" auricular pressure of 45–50 mm. of water and a mean pulmonary arterial pressure of 18 mm. Hg may be regarded as normal averages.

In eleven experiments, such pressure combinations were obtained by a low degree of pulmonary ventilation. A few typical waves are shown in Fig. 3.

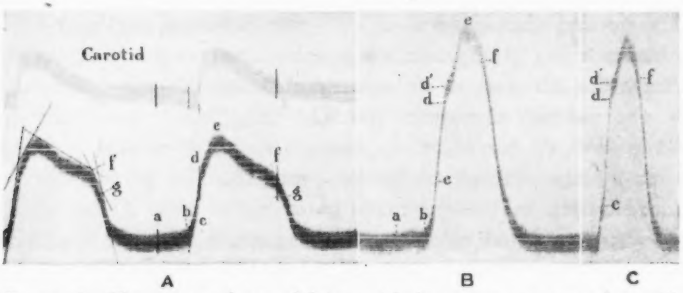


FIGURE 3. Three types of normal intraventricular pressure curves taken with manometers of different degress of sensitiveness. Detailed description in text. *a–b*, auricular systolic, *b–d*, isometric period, *d–f*, ejection period, *f–l*, diastole. Calibration line cut off.

The record in *A* was taken with a manometer in which a variation of 1 mm. was approximately equal to a like pressure change in the ventricle. The details of this curve are clear. Auricular contraction causes the slight rise of pressure from *a* to *b*. The tricuspid closure occurs in the confused vibration at *c*. The steep pressure rise during the *isometric period* (Anspannungszeit) follows from *c* to *d*. Here the semilunar valves open and the *ejection period* begins. This proceeds in two phases, viz., a rise of pressure (*d* to *e*) which is slower than that of the isometric period, changing after a rounded summit to the falling pressure (*e* to *f*). The closure of the semilunars causes the bend from *f* to *g*, after which the pressure drops rapidly in diastole. Attention may be called to the exact correspondence in contour between the ejection period and the arterial pressure curve upon which the corresponding relations are marked.

When the intraventricular pressure is recorded by manometers

in which 2 mm. of calibrated record represented approximately 1 mm. of intraventricular pressure change, the same details can be made out (Fig. 3, *B*). In these manometers there is a greater tendency to show superposed vibrations at the beginning of the ejection period (*d'*) and the closure of the tricuspid valves is also more clearly indicated. The two phases of the ejection period are still clearly recognizable. If, however, these records are recorded on slowly moving paper (Fig. 3, *C*) the existence of a broadened top is less clear to the eye. If, in addition, the manometer is damped, the jog at *d* is eliminated and a smoothly rounded curve similar to those of Straub is obtained. Close inspection still reveals evidences of all the angles illustrated in Fig. 3, *A*. (*Cf.* Straub's records.) Hence, while it may not be asserted that such records are wrong, it cannot be denied that they tend to obscure the details of the pressure variations as they actually exist and may readily lead to the erroneous conclusions formulated by Straub. Hence, whenever it becomes desirable to record such curves on slowly moving paper for special reasons, a careful scrutiny of the curve for its true details must not be neglected.

The Influence of Auricular Pressure on the Initial Intraventricular Tension and the Shape of the Pressure Curve. — Inasmuch as auricle and ventricle, during the diastole of the latter, are in free communication, it is commonly supposed that the intra-auricular and the *initial intraventricular pressures* (i.e., the pressure just before ventricular systole) are practically equal. Such is found to be the case when pressures are low. When, however, intra-auricular pressure increases, due to asphyxia or saline infusion, the initial intraventricular pressure deciphered from calibrated optical records (e.g., at *b*, Fig. 1), are progressively lower than auricular pressures measured by the water manometer.[1] The results, belonging to the curves shown in Fig. 4 and indicated in the following table in millimetres of water, are characteristic.

Intra-auricular pressure	24	32	54	90	130	150	190
Initial Intraventricular pressure	23.1	26.9	34.6	61.6	81.6	106.1	115.5

[1] For technic of measurement, *cf.* WIGGERS: This journal, 1914, xxxiii, p. 15.

Further experiments will be necessary to determine whether this may be attributed to the inferiority of a saline manometer in measuring these changes. For the present it is sufficient to direct attention to the fact that the figures of intra-auricular pressure given by the convenient saline manometer may not always be regarded as synonymous with the initial intraventricular tension.

The effect of changing the initial intraventricular tension [1] is exemplified by the transcribed curves shown in Fig. 4. As

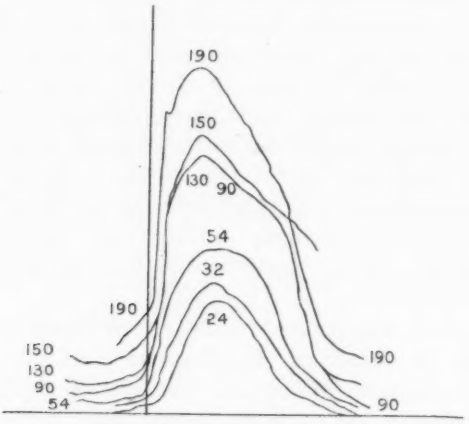


FIGURE 4. Effect of initial auricular pressure on initial tension and pressure curve. Numbers refer to auricular pressure.

the auricular and, consequently, the initial intraventricular pressure increased, the entire curve mounted higher. The steepness of the ascending limb increased, showing that it follows the law of the isometric curve established by Frank for [2] the frog's ventricle. The height of the isometric portion of the curve (i.e., the point *d*, Fig. 3), as in the case of the afterloaded frog's ventricle, is determined not only by its incline, but by its termination through opening of the semilunar valves.

[1] Lower pressures were produced by clamping the inferior vena cava or hemorrhage; higher pressures, as a rule, by saline infusion.

[2] FRANK: *loc. cit.*

The curves undergo a marked change in contour during the ejection period. With low initial pressures the top is quickly reached and the descending limb of the ejection period merges almost imperceptibly with the diastolic fall, giving the curve a simple rounded contour. As the initial pressure approaches normal, the top becomes broadened and more clearly divisible into its ascending and descending limb. This continues with very high auricular pressures.

Influence of Pulmonary Resistance. (*a*) **Clamping Pulmonary Vessels.** — By suddenly drawing tight a ligature previously placed around a large pulmonary branch, the resistance in the main pulmonary artery should be increased.

Previous investigators [1] have found such an increase in resistance of no recognizable importance for the intraventricular pressure. The curves of Fig. 5 indicate, however, that the maximal

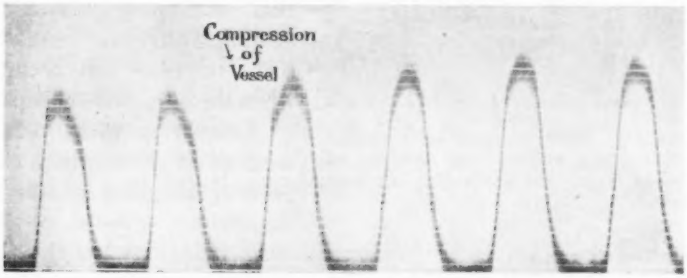


FIGURE 5. Effect of compressing lung vessel in the intraventricular pressure curve. Description in text.

pressure increases as the ligature is tightened. The initial tension remains unaltered and the steepness of the isometric period is consequently also unchanged, but the period ends progressively later as the compression continues.

The ascending limb of the ejection curve increases in height and reaches the summit later than before, that is, the peak is carried more toward the end of the ejection period. This indicates that the point at which the outflow exceeds the inflow of

[1] TIGERSTEDT: Ergebnisse der Physiologie, 1903, ii[2], p. 557.

the pulmonary artery occurs relatively later when the total resistance is increased.

(*b*) **Influence of Lung Inflation.** — In four experiments the lungs, entirely freed from their pleural attachments, were inflated to four degrees that may be described by the terms, (*a*) forcibly collapsed, (*b*) naturally collapsed, (*c*) mildly inflated, (*d*) strongly inflated. In the intraventricular pressure curves taken during these respective stages of lung inflation, typical changes took place, three examples of which are given in Fig. 6.

The initial intraventricular pressure and hence the steepness of rise remain unaltered. The isometric period terminates at a lower level when the lungs are most markedly inflated and within a shorter time interval. The greater the inflation, the more pointed the summit; or, vice versa, the more rounded top occurred when the lungs were collapsed.

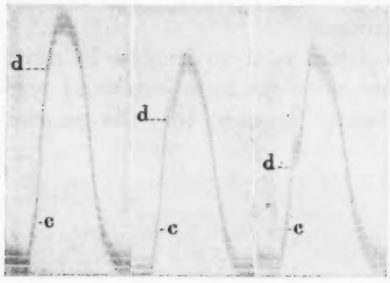


FIGURE 6. Three intraventricular pressure curves taken with (*a*) lungs naturally collapsed, (*b*) moderately inflated, (*c*) markedly inflated.

Comparing these records with those obtained by compressing the lung vessels the conclusion appears obvious that the *resistance in the pulmonary circuit decreases when the lungs are inflated*, and increases when they collapse. Attention may be briefly directed to the fact that this is contrary to current teaching as to the influence of lung inflation, but accords with the recent observations of Cloetta.[1]

Influences Modifying the Contractility of Cardiac Muscle. — It is obvious that any mechanism modifying the function of cardiac contractility may, independent of initial pressures and pulmonary resistance, modify the shape of the intraventricular pressure curve. Since such an action may occur as a result of therapeutic or pathological influences, and, probably, normally as well, it is important to study the nature of the influence.

[1] CLOETTA: Archiv für experimentelle Pathologie und Pharmakologie, 1911, lxvi, p. 409.

It was sought at first to test the influence of the vagus in this capacity. As a result of such stimulation it was found that all the results can most probably be explained as resultants of a changing initial tension and pulmonary arterial pressure. Inasmuch as not a sufficient number of experiments are at hand to rule out the possibility of such an influence occurring in unanaesthetized animals, they are not incorporated in this report.

Contractility may be conveniently modified by two internal secretions however. It may be augmented by adrenalin and depressed by pituitary extract.

(*a*) **Effect of Adrenalin.** — If adrenalin is introduced while the intraventricular pressure curve is recorded on a film that moves relatively slowly, it is found that, synchronously with the increase in rate, a reduction of the initial intraventricular pressure and an increase in the height of the curve take place. The *a–v* valves close at a somewhat lower intraventricular pressure, but the semilunar valves open only when a higher level is reached. The isometric period shows a steeper rise and occupies a shorter time *contrary* to what might be anticipated were the lower initial pressure alone concerned. It can only be inferred, therefore, that adrenalin directly modifies the contractility. After eight or ten beats the acceleration is superseded by a vagal slowing. The initial pressure becomes still lower, but the contractility effect keeps on increasing.

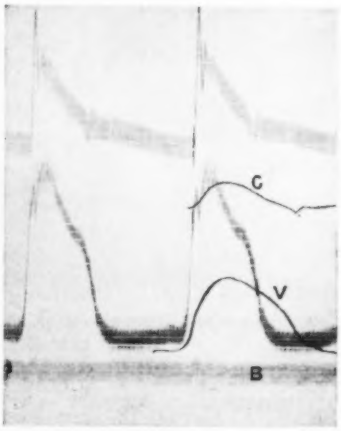


FIGURE 7. Comparison of the intraventricular and carotid after adrenalin compared with the same (sketched in) before.

These details of contour may also be discerned in the record of Fig. 7, over which (but relatively too near the base line) has been traced the curves *c* and *v* representing the respective carotid and intraventricular curves before adrenalin administration, They show clearly, furthermore, that whether or not vibrations

occur at the beginning of the ejection period and in the aorta depends largely upon the vigor with which the heart contracts and, since they are found normally in the carotid and pulmonary arterial pressure curves, it may be assumed that they occur also within the ventricle in the unopened chest. Unquestionably, as here, the depressing effect of anaesthetics and exposure of the heart may completely abolish these superposed vibrations from experimental records. Hence, the writer would not regard records such as are shown in Fig. 3, *A* — even when venous and arterial pressures are adequate — as entirely representative of those occurring normally, but as curves from a depressed heart. Only those

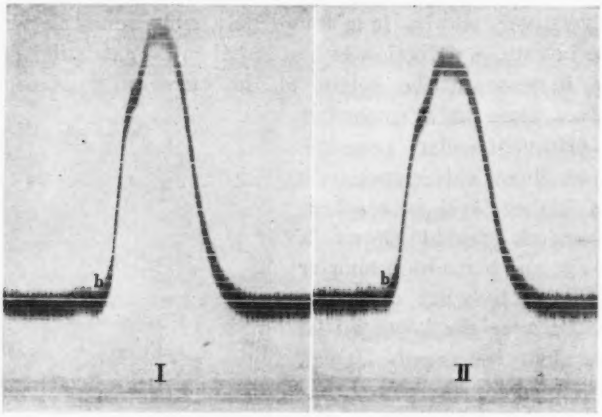


FIGURE 8. Two curves of intraventricular pressure before (I) and after (II) pituitary extract.

intraventricular pressure curves displaying oscillations at the beginning of the ejection may be regarded as showing normal contractility (e.g., Fig 3, *b*). Such curves only should be made the standard in studying pathological disturbances experimentally.

(*b*) **Effect of Pituitary Extract.** — The writer [1] has previously shown that pituitary extract, unlike adrenalin, decreases the amplitude of cardiac contractions. Inasmuch as this is contrary

[1] WIGGERS: American journal of the medical sciences, 1911, cxli, p. 508.

to the results obtained by Hedbom[1] and, more recently, by Werschinin,[2] its effect in intraventricular pressure is of interest. Two waves, one before, the other after pituitary action, are shown in Fig. 8. Synchronous with its slowing action it causes a decrease in the height of the pressure curve. In spite of an increase in the initial intraventricular tension measured at *b* the steepness of the isometric curve decreases and terminates at a lower pressure.

IV. Summary

1. When the auricular and pulmonary arterial pressures are approximately normal the pressure curves in the right ventricle, recorded by optical manometers of high vibration frequency, may be divided into (1) an auricular period, (2) an isometric period (period of rising tension) (3) an ejection period, during which the pressure rises, reaches a summit, and then slowly falls, and (4) a relaxation period (Fig. 1).

2. The *initial intraventricular tension*, i.e., the tension existing in the ventricle just before contraction, is not as great as auricular pressure when the latter is high, but, as both increase in the animal, the isometric curve becomes steeper and terminates later. The ejection period changes from a rounded to a broadened top with a higher summit and a clearer differentiation into an ascending and descending limb.

3. Increasing the pulmonary resistance by occluding a pulmonary branch causes an alteration neither in the initial tension within the right ventricle nor in the steepness of the isometric period, but prolongs this period of rising tension and causes a more rounded top in which the maximum is reached at a later time. As collapse of the lungs causes precisely the same changes as occluding the lung vessels, the deduction is made that *inflation of the lungs decreases and collapse increases the resistance in the pulmonary circuit.*

4. By modifying the contractility of the heart through adre-

[1] Hedbom: Skandinavisches Archiv für Physiologie, VIII, pp. 161–612, 1898.

[2] Werschinin: Ueber die Herzwirkung des Pituitrins, Archiv für die gesammte Physiologie, 1913, clv, p. 1.

nalin and pituitary extract and comparing these records with those obtained from deeply and lightly anaesthetized animals, the conclusion is arrived at that the presence and character of the superposed vibrations at the beginning of the ejection period, as well as those in the arteries, depend on the vigor of cardiac contractions. As the carotid and pulmonary arterial curves obtained with closed chest give evidence of such vibrations, they must also exist in the ventricle of unoperated animals. Such curves must, therefore, alone be regarded as entirely normal intraventricular pressure curves in spite of the fact that records free from them may be recorded when venous and arterial pressures are ostensibly normal.

THE NATURE OF FIBRILLARY CONTRACTION OF THE HEART.—ITS RELATION TO TISSUE MASS AND FORM[1]

By WALTER E. GARREY

[*From the Physiological Laboratory of Washington University, St. Louis.*]

IT is a noteworthy fact that the hearts (ventricles) of large animals fibrillate with great ease and only rarely recover from the fibrillary state, while small hearts rarely fail to recover. It was noted by McWilliam[2] that "spontaneous recovery may take place readily in the hearts of the cat, rabbit, rat, mouse, hedgehog, and fowl." The ventricles of dogs do not usually recover spontaneously from fibrillation, although they do so in rare instances, as noted by Porter.[3] The larger beef heart is one which enters into the fibrillary state with greatest ease and caprice. Erlanger[4] records this fact and states "that it is not often that fibrillation of the calves' heart can be stopped, as in other hearts, by means of temporary perfusion with potassium chloride solution." In this connection we may also refer to the well-known fact that fibrillation of the thin walled auricles is usually of a transitory nature, while that of the thicker ventricles of the same heart is much more prone to persist. It would appear obvious, from a consideration of these facts, that the size of the tissue masses involved in the process may have an important bearing on the induction of and recovery from the fibrillary state, yet, so far as we have been able to ascertain, these phenomena have never been systematically investigated from this viewpoint,

[1] The main features of this work were reported to the St. Louis Medical Science Club, November 12, 1912, and a synopsis appears in the Proceedings of the Society, Interstate medical journal, December, 1912, xix, p. 1081.

[2] J. A. McWilliam: Journal of physiology, 1887, viii, p. 296 *et seq.*

[3] W. T. Porter: This journal, 1898, i, p. 80.

[4] J. Erlanger: This journal, 1912, xxx, p. 400.

although Porter[1] found that he could suppress fibrillation of pieces of the heart more easily than the whole heart, and McWilliam[2] found that the isolated ventricular apices of all mammals worked with could recover from fibrillation again and again.

Our investigations give substantial support to the a priori view, based upon the above mentioned facts, that the ease with which the fibrillary process may be induced and with which spontaneous recovery from the fibrillary contractions takes place is inversely proportional to the mass of fibrillating tissue. In harmony with these facts is the finding that the extension of fibrillary process from any portion of the heart to another is dependent upon the cross sectional area of the conducting tissue connecting them. Our experiments support Porter's view that the essential nature of fibrillary contractions must be referred to abnormalities in impulse conduction — to the existence or establishment of blocks, or at least to relative differences in conductivity,[3] rather than to any peculiarity or alteration of contractile properties.

I. Experiments with Fibrillating Auricles

Any Small Auricular Piece will Cease Fibrillating.—When the auricles of cats, rabbits, or dogs are stimulated with strong faradic shocks, localized at any point, the whole musculature of both auricles enters into violent fibrillary contractions which usually persist for a time varying from a few seconds to several minutes, or more rarely for hours, after stimulation has ceased. In experiments conducted upon these mammals it was found that when a portion of the wall of fibrillating auricles was picked up by forceps and functionally separated from the heart by ligating, or by clamping with haemostatic forceps, the portion so separated ceased fibrillating at once, although the organ from which it was removed continued its inco-ordinated contractions unaltered. Such

[1] W. T. Porter: This journal, 1898, i, pp. 71–82.

[2] J. A. McWilliam: *loc. cit.*, p. 301.

[3] The block hypothesis originated with W. T. Porter: The journal of physiology, 1894, xv, p. 135; This journal, 1899, ii, p. 129; 1905, xiii, pp. xxiii and xxiv; 1905, xv, p. 5.

a procedure is especially applicable to the auricular appendices, and it was found that a whole appendix, either right or left, could be functionally removed in this way and would invariably stop fibrillating and come to complete rest. The appendices or other pieces could, subsequently, be removed by section and their properties studied.

The Excised Pieces Retain their Normal Properties.—It was important to determine whether pieces cut away from the fibrillating auricles had, as a result of their previous abnormality and removal from the heart, lost any of their physiological properties. It was found that they responded with a single normal co-ordinated contraction in response to a single mechanical or electrical stimulus. When the stimuli were repeated regularly a rhythmic response was elicited. Many of the pieces removed in the above experiments were immediately placed in warm (40° C.) sodium chloride solutions, or in Ringer's mixture, and all beat with perfect rhythms.

The normal functional capacity of the quiescent portions of the fibrillating auricles was strikingly illustrated by experiments of the following type: The heart of a dog was exposed and the auricles made to fibrillate by faradizing the tip of the right auricular appendix. The left appendix was then clamped off with a flexible intestinal clamp, the jaws of which were covered with rubber tubing. Compression was carefully graded to avoid any crushing injury and, as it increased in degree, fibrillation was seen to be supplanted by irregularly recurring co-ordinated contractions, the appendix finally coming to rest when block was complete. When the clamp was suddenly released, the appendix gave a few co-ordinated contractions and then fibrillated. These procedures could be repeated as many times as desired with the same results. The experiment became at once more striking and significant when the clamp was gradually released, for it was possible, in such cases, to obtain a degree of compression with which the appendix was kept beating in a perfectly co-ordinated manner, although irregularly. With further decompression these contractions passed over into a mere flutter and then fibrillation ensued. In two experiments the whole atrium assumed its normal rhythmic contractions while the clamp was in position and the appendix

was at rest; upon releasing the clamp the appendix beat as in partial block, later taking up the rhythm of the heart.

It is obvious from these experiments that pieces of auricular tissue possess normal capacity for rhythmic contractions when functionally separated from the fibrillating auricles. It is also clear that when connected normally they may fibrillate in response to an irregular shower of impulses which originate in the fibrillating auricular mass; when the number of these impulses is decreased by clamping, the piece may beat co-ordinately in spite of the inco-ordination of the auricular tissue with which it is connected.

The Fibrillary Contractions are not Sustained from the Point faradized in Initiating them. — Fibrillation has been looked upon as an inco-ordination which results from the fact that the irritability of certain areas is increased to such an extent that they become independently and highly rhythmic. In such a view the inco-ordination resolves itself into a response to extra-systole formation (Lewis).[1] Since faradization localized to a circumscribed area may precipitate the fibrillary process, it would seem logical to assume, as McWilliam[2] did, that the fibrillary contractions started in and were sustained from this area. This view would seem the more plausible since recent work has demonstrated that faradization of auricular tissue markedly increases its rhythmicity and force of beat (Erlanger).[3]

To test the validity of this idea of the nature of fibrillation a series of experiments was instituted to determine whether, after inducing fibrillation by stimuli localized within a very circumscribed area, the process persisted because impulses were continuously and inco-ordinately sent out from this area. The experiments were conducted along the lines of those described above. The tip of one auricular appendix was faradized until sustained fibrillary contractions were instituted, after which this appendix was functionally separated from the fibrillating auricles either by ligating, cutting, or clamping. As a result of this procedure the appendix came to rest, but the auricles invariably continued their delirium unaltered. The stimulated appendix behaved exactly

[1] Thos. Lewis: Heart, 1910, i, p. 353.
[2] J. A. McWilliam: *loc. cit.*, p. 309.
[3] J. Erlanger: This journal, 1910, xxvii, p. 102.

as any other portion of the auricles behaved when removed in a similar way.

Fibrillary contractions, then, are not dependent upon impulses initiated in any given area, even if the area be the one from which the process was started, but is a process in which the whole tissue mass is involved. It is dependent upon the integrity of a considerable mass of tissue, and subdivision of this mass into smaller bits brings all of the tissue out of the state of inco-ordinated contractions, the pieces either coming to rest or beating independently with a perfect rhythm depending upon the portion of the heart from which they were removed and upon the conditions to which they are subjected.

II. Experiments with Fibrillating Ventricles

Effects of Subdivision of Ventricles.—Any extended study of the relation of mass to fibrillary contractions is impossible with the hearts of cats or rabbits, owing to their well-known tendency to recover spontaneously from this condition, a tendency which may be due, at least in part, to their small size. It was determined, however, that cutting these small ventricles into two or four pieces would stop fibrillation immediately. More extended observations were conducted upon the ventricles of dogs, in which persistence of the fibrillary contractions is the rule. The results of subdivision of the ventricular tissue were independent of the cause inciting to fibrillation, i.e., whether the process was started by mechanical stimuli, by faradization, or spontaneously after the injection of digitalis, salts of barium and calcium, or other drugs.

Pieces were shaved from the wall of the fibrillating left ventricle by a cut parallel to the surface, the cut being so made that the cavity of the heart was not entered. These pieces ceased fibrillating at once, although some were two centimetres wide and four centimetres long, and as thick as could safely be made. In other instances the whole of the apices were removed by cut, clamp, or ligature after the manner described above for the auricular appendix. The piece thus removed always came to rest while the main fibrillating mass of the ventricles continued its abnormal

delirium. When pieces were cut away from the fibrillating ventricles it was noted that, like the apex, they ceased their incoordination and it was immaterial whether the pieces came from the walls of either ventricle or from the septum; they all behaved in identically the same way, provided they were of the same size.

It was noted, however, that larger pieces might fibrillate several seconds, or even half a minute after removal, while small bits ceased immediately. Pieces of equal surface area but including the whole thickness of the wall of the left and right ventricles, respectively, showed distinct differences in the time of persistence of the fibrillary contractions after removal; the thicker pieces taken from the left ventricle always fibrillated for a longer period before coming to rest. That the persistence of fibrillation is in direct proportion to the mass of the tissue is also indicated in the following type of experiment: Two cuts were made in the ventricle on either side of the septum and extending from the apex to the auriculo-ventricular ring, thus dividing the fibrillating heart into three pieces, the thin wall of the right ventricle, the thicker septal and left ventricular pieces. The two thick pieces continued to fibrillate, but the thinner right ventricle stopped within fifteen seconds. Additional cuts dividing each of the two fibrillating masses into two equal parts brought all the fragments to rest.

It was clear, from the numerous experiments made, that any piece cut from any part of the mass of ventricular tissue would cease fibrillating if small enough, e.g., if its surface area was less than four square centimetres. As was indicated for auricular tissue, even the portion to which the localized faradic stimuli had been applied in starting the fibrillary contractions could be excised and would come to rest while the remaining mass would fibrillate. A large part of the septum, when excised, acted in a similar way. Thus in the case of the ventricles, as with that of the auricles, fibrillation involves the whole tissue mass and is not dependent upon impulses coming from any single area of the tissue, nor is the recovery from the condition dependent upon any co-ordinating centre within the tissue (e.g., the septum), for any piece can recover.

Properties of Pieces Excised from Fibrillating Ventricles. — Quiescent pieces which have been excised from the fibrillating

ventricles of the dog are capable of responding with co-ordinated contractions when stimulated and will beat rhythmically when placed in warm M/6 solutions of sodium chloride. After recovery due to diminishing the size of the fibrillating mass, the pieces are also capable of responding to the normal physiological stimulus as the following experiment will indicate. By faradization the ventricles were made to fibrillate, in which process the auricles did not participate, but beat with their own rhythm, interrupted, however, by extra-systolic irregularities due to retrograde ventricular impulses. From the ventricles bits the size of a chestnut were removed piecemeal beginning at the apex. Each piece upon removal became quiet. When approximately three-fourths of the ventricle had thus been removed piecemeal, the remaining basal ring suddenly ceased fibrillating and beat in regular sequence with the auricles, indicating its return to relative normality. That, in this experiment, so large a mass of ventricle as one-fourth of the whole should have spontaneously ceased fibrillating may have been related to the fact that it was the basal portion with the shape of a ring (the importance of such a shape will appear in a subsequent section), or it may have been due in part to a slight cooling, which, as indicated by Porter's experiments, favors recovery; but the point of chief importance to us lies in the fact that so long as the mass was larger than one-fourth, fibrillation did not cease, while small pieces cut from it, and obviously of the same temperature, recovered immediately.[1]

[1] It should be emphasized that our method throughout has been one in which the relations of tissue mass and shape to the fibrillary contractions were determined upon tissues under like conditions; for example, the pieces compared had the same temperature as the fibrillating mass from which they were removed, yet they did not fibrillate. On the other hand the results were made doubly striking by the cessation of fibrillation in pieces which were transferred immediately to physiological saline solutions, the temperature of which was distinctly above that of the pieces. High temperatures have been shown by McWilliam (J. A. McWilliam: Journal of physiology, 1887, viii, p. 303) to increase the tendency to fibrillate. In our experiments, in which a clamp was applied to the auricle and alternately tightened and released to show cessation of fibrillation of the auricular appendix, and in similar experiments with ventricular tissue, as noted below, no question of differences in temperature can enter, and this is, of course, true in the experiments with the various turtle hearts.

In testing the reaction of pieces cut away in the above experiments faradic shocks were used in some instances. In these tests we obtained the significant result that very small pieces fibrillated only during stimulation, while larger pieces fibrillated for several seconds, or more, the duration of the fibrillary condition being in direct proportion to the mass of the tissue, emphasizing in another way the result obtained by the method of excision.

The Relation of Shape to Persistence of Fibrillation.—In performing the experiments described in the preceding paragraph, it was noticed that when faradic stimuli were applied to detached narrow strips several centimetres in length, the fibrillary contractions were confined to the region about the electrodes, but that the tissue at the other end of the strips beat co-ordinately, although irregularly. All contractions ceased when stimulation was stopped. This experiment suggested at once that fibrillation was impossible in sufficiently narrow strips.[1] This suspicion was at once justified when a fibrillating mass, such as the entire right or left ventricle or septum, was so incised as to make a trouser or trident preparation with individual parts connected by narrower bridges. Fibrillation ceased in such a preparation and faradization of one component always resulted in co-ordinate contractions of the other components. Similarly, it was found that when a cut was made into the apex of the fibrillating ventricles and continued spirally in such a manner as to produce a strip with a width of approximately one centimetre, the distal end of the strip would beat co-ordinately in response to irregular impulses coming from the fibrillating mass at its proximal end. It was possible to continue the incision and to progressively incorporate more and more of the fibrillating mass into the strip until, in some instances, it reached a length of thirty or even fifty centimetres. For a short time perfectly co-ordinate waves could be seen traversing the whole length of these strips. With the progressive reduction of the size of the fibrillating mass it was found that upon reaching a certain limit fibrillation ceased and beats, co-ordinate with the auricular contractions, intervened. The development of blocks in these strips will always take place sooner or later to interfere with the ideal picture just presented.

[1] J. Erlanger: This journal, 1910, xxvii, p. 99 *et seq.*

Owing to the rapid succession of impulses it is not always easy to determine whether the contractions of such strips are co-ordinated or not. Two procedures quickly revealed the true nature of the conditions; first, gentle compression of the proximal end of the strip established the condition of partial block and, by this means, the contraction waves could be made to progress down the strip with any desired intervals; second, single stimuli applied to the strip produced in it well-marked extra-systoles, which cannot be detected in fibrillating cardiac tissue.

In some instances success attended efforts to cut these strips, beginning at the apical portion of the ventricles, without precipitating the ventricles into the fibrillary state. The application of faradic stimuli to the strip produced inco-ordination in the region of the electrodes, but in no instance did this manipulation result in fibrillation of the ventricular tissue to which the strip was attached; it beat co-ordinately, rapidly, and with a surprisingly regular rhythm.

Conduction of the Fibrillary State.—It has been firmly established by the work of Vulpian and others [1] that in the mammalian heart the fibrillary state is not transmitted from fibrillating auricles to ventricles, or from fibrillating ventricles to auricles, but that the structures not participating in the delirium may contract as a whole and in a perfectly co-ordinate manner.

In the explanation of the fact that the fibrillary state is not transmitted through the auriculo-ventricular bundle, it might seem warrantable, in the absence of experimental data, to attribute it to special physiologic properties of the tissue composing the bundle, to the fact, for example, that contractility has not yet been demonstrated for Purkinje tissue unmixed with muscle cells.[2] On the other hand it is possible that the narrowness of this conducting isthmus may suffice to account for its relation to the spread of the fibrillary process.

[1] VULPIAN: Archives de physiologie, 1874, p. 976. W. T. PORTER: This journal, 1898, i, pp. 77–81. ERLANGER and HIRSCHFELDER: This journal, 1906, xv, p. 167. CUSHNEY and EDMUNDS: American journal of medical sciences, 1907, cxxxiii, p. 74 *et seq.* W. E. GARREY: This journal, 1908, xxi, p. 287.

[2] J. ERLANGER: This journal, 1912, xxx, p. 405.

That the latter view is the probable one is indicated by the behavior of narrow strips as described in the previous section; that it is the correct one was easily proven by direct experiments in which only a narrow isthmus of muscle was left between portions of the auricles in order to determine whether fibrillation could pass from one side to the other. The following abbreviated protocols give the results of the experiments.[1]

Dec. 16, 1912. — The heart of an etherized cat was removed and perfused through the aorta and coronary arteries with Locke's solution (without glucose or oxygen). A cut was made between the auricles in the anterior part of the vault to the left of the septum. This cut was extended until a distinct delay in the passage of impulses from the right to the left auricle was noticed, then very carefully extended until a permanent partial block for normal impulses was induced. Faradization of the right auricle produced fibrillation which continued for a short time after faradization was stopped. The fibrillation did not involve the left auricle, which beat co-ordinately but irregularly. In similar manner fibrillation of the left auricle, which lasted only during the period of stimulation, did not extend to the right auricle across the connecting isthmus of muscular tissue. Owing to the ready recovery of co-ordinated contractions in these auricles the same experimental results were repeatedly obtained.

Dec. 18, 1912. — Artificial respiration was established on a large etherized cat. The heart was exposed by cutting away the anterior chest wall. With heavy-jawed haemostatic forceps the auricular tissue, at the left of the pulmonary veins, was crushed in a line so directed that a little more than the left appendix was separated from the auricles except for a narrow isthmus of normal muscular tissue, in which there was evident delay in the passage of impulses from the right to the left appendix. Fibrillation of the right auricle outlasted the causative faradization for a short time, but the left appendix continued to beat co-ordinately, although irregularly. Fibrillation of the (smaller) left appendix ceased when the causative faradization was stopped. During fibrillation of the left appendix, the right side of the auricles beat co-ordinately but irregularly.

[1] I am indebted to Dr. J. Erlanger for helpful co-operation in the performance of these experiments.

It is obvious from these experiments that a narrow bridge of normal auricular tissue behaved, so far as conduction of fibrillation was concerned, just as does the narrow auriculo-ventricular bundle.

The author extended these observations to the ventricular musculature of the dog, where permanent fibrillation is the rule. It was found that a sufficiently narrow bridge of tissue (a strip somewhat less than a centimetre wide was usually found to be sufficiently narrow) [1] left connecting the basal and apical halves can conduct normal impulses but will prevent the extension of fibrillation from one piece to the other, although individual impulses do pass and produce, at irregular intervals, contractions of the apical piece when the basal portion of the ventricles is fibrillating, or extra-systoles in the basal portion when the apical portion is fibrillating. In two of the experiments the ventricles were divided into two approximately equal masses, an apical and a basal portion, connected only by the moderator band. The results with this natural isthmus of normal muscular tissue were the same as those quoted above and need not be described in detail.

These experiments prove conclusively that it is impossible for the fibrillary state to be transmitted across a sufficiently narrow conducting bridge to non-fibrillating muscle; they offer the most obvious explanation of the fact that in the mammalian heart fibrillation does not extend through the His bundle, either from the auricles to ventricles, or in the reverse direction. It is not necessary to refer this property to any specialization or differentiation of the tissue or to any anatomic peculiarity other than the narrowness of the conducting bridge.

[1] The degree of narrowing necessary to prevent the extension of fibrillation will, naturally, vary with the physiological condition of the muscle. It would seem probable that the more irritable the tissue, the narrower the bridge must be; thus it was found by Porter (This journal, 1899, ii, p. 132) that fibrillation did extend across a very small muscular bridge, but that in other hearts it did not, "probably because the power of conduction in the bridge was too much reduced." Our clamping experiments show conclusively that the extension of the fibrillary process may be prevented in a bridge of any width when the conductivity is decreased by compression, although it is possible in such cases to still have some of the impulses pass the region of block and produce co-ordinate contractions.

III. Experiments with the Hearts of Turtles

The hearts of cold blooded animals are subject to inco-ordinated contractions which have been referred to in various terms, such as "undulatory movements" (Gaskell), "inter-vernucular action" (Mills), and by German writers as "Wogen und Wühlen." Bätke [1] has concluded, and we agree with him, that these are all true fibrillary contractions. We have repeated the procedures, which have been described above, in our work with mammalian hearts upon the hearts of large Pseudemys elegans. In the winter state of these hearts the inco-ordinated contractions of both auricles and ventricles are easily induced by faradization or by repeated or long continued vago-sympathetic stimulation, especially after the administration of atropine. It would be a needless repetition to detail the experiments; suffice it to say that in the recovery of the heart when subdivided, and in the relation of narrow strips and bridges of tissue toward conduction of the inco-ordination, the behavior of such hearts was identical with that of fibrillating mammalian cardiac tissue — an indication that the cardiac inco-ordinations are indeed true fibrillations.

What appears to be a striking example of the fact that large masses of tissue fibrillate more easily and recover less readily from the fibrillary state, is seen in the behavior of the ventricles of the large marine loggerhead turtle. Mills [2] noted the tendency of these hearts to fibrillate, and our experience indicates that it is indeed difficult to manipulate them in situ, or to remove them from the animals without precipitating the fibrillary contractions of the ventricles, although the auricles continue beating co-ordinately. Recovery from fibrillation may take place spontaneously, but not invariably, and the fibrillary process usually persists for a long time. When such ventricles are cut into centimetre cubes, these bits stop fibrillating, although they frequently contract rhythmically in the blood serum for several minutes before coming to rest. When stimulated by a few mechanical stimuli or faradically they contract rhythmically again but do not fibrillate. The

[1] H. Bätke: Archiv für die gesammte Physiologie, 1898, lxxi, p. 412; also *cf.* Langendorf: Archiv für die gesammte Physiologie, 1895, lxi, p. 314.

[2] T. W. Mills: Journal of anatomy and physiology, 1887, xxi, p. 1.

greater excitability and rhythmicity of these hearts may be in part responsible for the fibrillary tendency, but this factor only accentuates the importance of the mass factor. The large size, slow conductivity, and relative independence of vascular nutrition, as compared with the mammalian heart, coupled with the pronounced tendency to fibrillate, made it feasible to conduct upon the ventricles of marine turtles some experiments which have a fundamental bearing on the nature of the fibrillary contractions.

The Ring Experiment.—It was found that rings, two centimetres broad, cut from the base of the fibrillating ventricles of large loggerhead turtles did not recover from the fibrillary contractions. A most striking phenomenon resulted when such broad fibrillating rings were narrowed by incising midway between the outer and inner margins, the incisions in these cases not being carried completely around the ring. In this way, by separation of the inner and outer portions, a figure 8 was formed, the two loops being connected by the broad fibrillating isthmus; a second cut across this mass connecting the inner margins of the two loops converted the tissue into a single large ring one centimetre broad and from six to ten centimetres in diameter. As soon as this narrowing was completed it was found that the inco-ordinated fibrillary contractions had resolved themselves into a number of contraction waves which followed each other successively and repeatedly around and around the ring, all progressing in the same direction, an exhibition to which we may apply the term "circus contractions."[1] It usually so happened that the number of contraction waves gradually decreased until but a single contraction wave was left repeating its circuit again and again. In one instance such a wave continued around the ring for seven hours, making each circuit in from six to seven seconds, the diameter of the ring being ten centimetres. When such waves died out new ones were easily started by single mechanical stimuli. Faradic

[1] These experiments were conducted and publicly demonstrated at Woods Hole, Mass., before the appearance of the paper of R. G. MINES (Journal of physiology, 1913, xlvi, p. 349). Our rings were, however, cut from fibrillating tissue, which makes the results especially significant for the interpretation of the nature of the fibrillary process. Our conclusions are, in many respects similar to those of Mines (*l. c.*, p. 373).

stimuli did not cause fibrillation, but started a succession of waves, the number and distance between them being dependent upon the rate of progression and the duration of the refractory phases.

Experiments of this nature prove conclusively that fibrillary contractions are in reality normal in character when progressing along a narrow path, and that the abnormality is dependent upon the presence and relative complexity of the bypaths available. Romanes [1] studied the passage of impulses in rings of contractile tissue cut from the umbrella of the cover eyed medusa (Aurelia), and his studies have been extended by Mayer [2] working with the jelly fish (Cassiopea xamachana). The latter investigator has shown that by properly grading the compression applied to a ring near the point of stimulation, it is possible to block the progress of the contraction wave passing in one direction from the point stimulated, and by release at the proper moment to allow the wave which took the opposite course to continue its progress about the ring. By repeating the manoeuvre a number of waves, all making the circuits in the same direction, were started by what may be called the method of block.

Now the presence of blocks is exactly what we noticed in our ring preparations of the turtles' ventricles. The blocks, however, had developed spontaneously and affected the contraction waves passing in one direction only; those moving in the opposite direction passed the region of block and continued their progress about the ring. It was thus possible by simply touching the tissue at a point near the region of block to add a new wave to those already present.

The causes underlying the unidirectional selection by such blocks is not altogether clear, but appeared to be related to the irregular width of the strips on either side of the points of blocking, and consequently to differences in strengths of the impulses passing a given point of block. Be this as it may, the fact remains that spontaneous blocks of this type do appear, and, in our opinion, this fact is of greatest importance for any adequate theory of fibrillation. Furthermore, the close examination of these ring

[1] G. J. Romanes: Jelly fish, star fish and sea urchins, 1885, p. 67.

[2] A. G. Mayer: Popular science monthly, December, 1908, p. 481.

preparations revealed the equally important fact that *shifting* points of block are easily distinguishable. If, for example, a given area of the ring be closely watched each time the contraction passes it, it will often be found that at one time, only the tissue of the outer edge contracts and transmits the wave, while the inner edge remains quiescent. The next wave, however, may involve the inner margin, but the outer may not contract; or upon another circuit closest scrutiny reveals no superficial evidence of contraction, yet a wave of contraction may be seen to emerge again beyond the quiescent region and to proceed as if no obstruction had been offered to its progress; in reality none had been offered — the contracting elements were simply obscured by others which did not contract. In the very next circuit this same region may contract with all the appearances of normality. We possess in these observations the visible record of one of the fundamental phenomena of block which apparently are the cause of fibrillation.

IV. The Nature of the Fibrillary Process

For a complete refutation of the idea that fibrillation is due to the destruction of a co-ordinating centre (Kronecker), the work of McWilliam and of Porter has been conclusive. Our experiments amplify the proofs they have adduced.

That in the fibrillary process there is altered conductivity was clearly stated by McWilliam in 1887 (*loc. cit.*). We believe, however, that experiment does not confirm the view that the fibrillary process is sustained by new impulse formation in tissue of heightened excitability, a belief which also includes the more recent statement of this view by Lewis, who looks upon fibrillation as the result of extra-systole formation. Fibrillation of cardiac tissue may be induced by a sharply localized faradization, and while it is certainly true that the result of such stimulation is to raise the excitability with the possibility of extra-systole formation, our experiments have shown conclusively, however surprising the result may be, that the fibrillary process is not sustained by impulses arising in the portion of the tissue directly stimulated, for these portions may be removed without stopping the inco-

ordination, and once started, fibrillation may continue for a long time in tissue remote and physiologically isolated from the point stimulated.

Concerning the probable nature of the fibrillary process, Porter in 1894 made the following statement: "Fibrillar contractions of the heart may be due to an interruption of the contraction wave. The contraction wave would thus be prevented from running its usual course, and the normal co-ordinated action of the ventricular cells would give place to the confusion conspicuous in fibrillary contractions."

The results of our investigation are in complete harmony with and add substantial support to this block hypothesis. The experiments which we have described above brought out the fact that fibrillation could not persist in small pieces, which, however, were still large enough to be the seat of blocks. In explanation of this fact and of the fact that larger masses do fibrillate persistently, the following conception seems to be adequately supported by experimental data.

Normally the impulse to contract does not spread throughout the whole musculature from fibre to fibre, but is delivered simultaneously to many different parts of the musculature of the ventricle from the auriculo-ventricular conducting system. The probability of this condition was pointed out by Tawara [1] and the electrocardiographic studies of Erfmann [2] indicate the correctness of the surmise. The musculature of the ventricles thus beats apparently as a unit but in reality as a group of isolated segments each of which receives its impulse from a different branch of the conducting system. When, however, the stimuli are applied to the musculature directly, as in the induction of fibrillation, the transmission is from muscle fibre to muscle fibre and a distinct time interval elapses between the contractions of different portions of the structure. (This has also been shown to be the case by Erfmann, (*loc. cit.*). From the point stimulated the impulses can spread in any and all directions, their progress being limited only by the pre-existence or development of localized blocks within the tissue mass. Such blocks divert the impulse into other and

[1] S. Tawara: Das Reizleitungssystem des Säugethierherzens, 1906, p. 187.
[2] Wilh. Erfmann: Zeitschrift für Biologie, 1913, lxi, pp. 155–182.

more circuitous paths and the area so blocked off can participate in contraction only when an impulse which has passed to other portions of the ventricle approaches it from another direction; this area thus in turn becomes the centre from which the progress of contraction is continued, to be in its turn diverted by other blocks. The existence of such blocks, and especially of blocks of transitory character and shifting location, has been noted in the experiments detailed above. These conditions make possible the propagation of the contraction wave in a series of ringlike circuits of shifting locations and multiply complexity. It is in these "circus contractions" determined by the presence of blocks, that we see the essential phenomena of fibrillation.

In small masses of tissue blocks may exist, but the time necessary for the impulse to traverse all available circuits is within the refractory period and the mass contracts as a unit and fibrillation is thus impossible. In larger masses this is not true, for the larger the mass the greater the possible number and length of the circuits, and the greater the probability that each impulse will circulate until it reaches tissue which has once contracted but has passed out of the refractory state; thus a continuous circulation of impulses is inaugurated, which is fibrillation. Such a mechanism would account for the greater liability of large hearts to fibrillate and for the greater persistence of the fibrillary state in large tissue masses.

It is conceivable that the establishment of relative differences in excitability and conductivity in different parts of the musculature without the condition of absolute block might result in the same phenomena of "circus contractions" and fibrillation. Thus inequalities in temperature or unequal action of such drugs as digitalis or barium salts may precipitate fibrillation in some such manner, although we venture the suggestion that the action of the latter in inducing this state of inco-ordination will be found to lie in their well-known tendency to produce blocks. There is evidence at hand which indicates that this view of fibrillation is in complete harmony with the effects produced upon the fibrillary state by vagus stimulation.

SUMMARY

The persistence of cardiac fibrillation is, other conditions being equal, directly proportional to the size of the tissue masses involved whether the pieces are cut from hearts already fibrillating or are faradically stimulated to start the process in them. The form of the tissue is important; for long narrow or thin pieces recover promptly, and narrow strips when connected with a fibrillating mass or when faradically stimulated do not fibrillate, but beat co-ordinately. Tissue rings cut from fibrillating hearts of marine turtles ceased fibrillating, but the contraction waves continued, repeating the circuit about the ring in co-ordinate "circus contractions." Sufficiently narrow bridges of any portion of the musculature of auricles or ventricles will prevent the extension of the fibrillary process and act thus like the auriculoventricular conducting bundle. When fibrillation is induced by localized faradization this locus may be subsequently excised, its inco-ordination will cease, just as will that of any other piece of similar size, while that of the remaining (larger) mass will continue, showing that the process, therefore, involves the whole tissue mass and is not sustained by impulses arising in any definite location.

The experiments support the block hypothesis and suggest that the blocks probably result in intramuscular ringlike circuits with resulting "circus contractions" which are fundamentally essential to the fibrillary process. Such ring circuits can exist in large masses but not in sufficiently small ones.

VARIATIONS IN THE SENSORY THRESHOLD FOR FARADIC STIMULATION IN NORMAL HUMAN SUBJECTS

II. The Nocturnal Variation

By E. G. MARTIN, G. H. BIGELOW, and G. B. WILBUR

[From the Laboratory of Physiology in the Harvard Medical School]

IN the first communication of this series[1] a rhythmic variation in electro-cutaneous sensibility between the hours of 8.30 A.M. and 8.30 P.M. was described, and was shown to agree with variations in ergographic fatigue and in reaction time over the same period. Because there is this agreement among these quite dissimilar manifestations of nervous activity, the conclusion was drawn that they all depend upon the condition of the nervous mechanism as a whole. In other words, the variations in sensory threshold are of central rather than peripheral origin, and the threshold itself is a useful criterion of the condition of the nervous system. The present paper is an extension of the observations to cover the period between 8.30 P.M. and 8.30 A.M.

Method. — The sensory threshold was determined according to the method of Martin, Porter, and Nice,[2] in which liquid (saline) electrodes are used and the threshold stimulus is measured in β units.[3] The β units are obtained by computation from the Z units of Martin (*loc. cit.*). The latter are found by observation, in a properly calibrated inductorium, of the position of the secondary coil at which threshold stimulation is obtained when a current of known amperage is broken in the primary circuit. For calculating β several values of Z must be determined with different, known resistances in the secondary circuit. The

[1] Grabfield and Martin: This journal, 1913, xxxi, p. 300.

[2] Martin, Porter, and Nice: Psychological review, 1913, xx, p. 201.

[3] Martin: The measurement of induction shocks, New York, 1912, p. 76. See also Grabfield and Martin: *loc. cit.*, p. 301.

electrical resistance of the tissue undergoing stimulation must also be determined.

One of us (Wilbur) has worked out a useful simplification of the computation for β, which is as follows: The original equations of Martin are $\beta = \frac{ZA}{R+A}$ and $A = \frac{Z_r R' - Z_{r'} R}{Z_{r'} - Z_r}$ in which R is the resistance of the secondary circuit when it includes only the secondary coil and the stimulated tissue, and R' the resistance of the same circuit after the inclusion of a known additional resistance; and Z_r and $Z_{r'}$ are the values of Z at resistances R and R' respectively. At least three values of Z_r for three different added resistances are always determined. If the expression for A is substituted for A in the equation for β above, and the resulting expression simplified, we have:

$$\beta = \frac{Z_r R' - Z_{r'} R}{R' - R}.$$

By adopting the expedient of using for the additional known resistances round numbers exclusively, as 10,000, 20,000, and 30,000 ohms, the denominator of the above expression becomes very simple and the solution of the entire equation not at all laborious. We have found the engineer's slide rule an indispensable aid in carrying out our numerous computations.

Observations. — Our conclusions are based on five series of observations on three different subjects. For one of these series we are indebted to Mr. Grabfield, who has kindly allowed us to incorporate with our own results an experiment carried out by him during the course of the study which was reported as the first paper of this series.[1] We should not feel justified in reporting so small a number of experiments were not the results rather unexpectedly concordant and reasonably in harmony with prevailing views as to the nocturnal state of the human nervous mechanism.

The experiments were carried out on the nights of July 13–14, 1912; July 9–10, 1913; and September 6–7, 1913. They could not well be made to conform to precisely similar conditions, therefore a brief description of each experiment is here given.

[1] GRABFIELD and MARTIN: *loc. cit.*

The experiment of July 13–14, 1912, had as subject a medical student, Bk, a young adult in good health. His sensory threshold was determined hourly from 4.30 P.M. During the intervals between stimulations he smoked cigarettes, read reclining, occasionally walked about. His evening meal was taken at 7.00 P.M. At 10.50 he went to bed, but did not sleep until after a threshold determination at 11.30. Between 11.30 and 6.30 the following morning the subject slept quite continuously, except during the taking of readings. When the time for a reading arrived he was wakened, bathed his head and hands in cold water, and the determinations were made as promptly as possible. The period of wakefulness did not exceed fifteen minutes in any case. Readings were taken at 12.30 P.M. and then at two-hourly intervals until 8.30 A.M.

In the experiments of July 9–10 and September 6–7, 1913, Bg. and W., healthy young medical students, acted alternately as subjects and observers. In the experiment of July 9–10 Bg. remained awake throughout the night. He occupied the intervals between determinations in computing the results of previous determinations and in reading. He smoked cigarettes occasionally. Subject W. was awake until midnight and slept during the intervals between determinations from that time till morning. He smoked two cigarettes early in the evening and one after waking in the morning. Threshold determinations were made hourly throughout this night. The procedure was as follows: At the proper time W. was wakened and went immediately to the room in which were the stimulating electrodes. His thresholds and tissue resistance were determined by Bg. as swiftly as possible; they were usually completed within five minutes from the time of waking. He then was replaced by Bg. whose thresholds were determined in like manner, W. acting as operator. At once after completing this second series of readings W. returned to his bed and fell asleep promptly. The entire waking period did not much exceed ten minutes.

On the night of September 6–7 both subjects slept between midnight and morning, being awakened at two-hourly intervals for threshold determinations by means of an alarm clock. The procedure was similar to that of the preceding experiment in that

W. acted each time as subject immediately after wakening and then made readings upon Bg. Both subjects went promptly to sleep after the determinations were completed.

Results. — The data obtained from the five experiments are given in Table I. Under each experiment the actual thresholds in β units are given in the first column, and the values of reciprocal $\beta \times 10^4$, adopted by Grabfield and Martin [1] as indices of irritability, in the second column. By examination of the figures representing irritability in the second column of each experiment the facts appear upon which this report is based. There was in general a decline in irritability during the evening from an early high point noted by Grabfield and Martin (*loc. cit.* p. 307) and confirmed by our observations. In each of the experiments there was a point of low irritability between 11.30 P.M. and 1.00 A.M., followed by some degree of recovery; and in four of the five experiments there was a second low point between 4.00 and 5.00 in the morning.

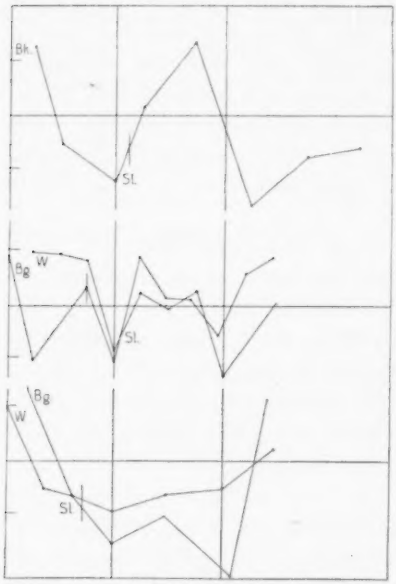


FIGURE 1. Nocturnal variations of irritability. No. 1, experiment of July 13–14, 1912. No. 2, experiment of July 9–10, 1913. No. 3, experiment of September 6–7, 1913. Individual irritabilities are represented in terms of percentage variations from average irritability. The extended abscissae are drawn at the level of average irritability. The extended ordinates indicate an interval of four hours. A short ordinate on each curve indicates midnight. The onset of the first sleep of the night is indicated by *Sl.*

To make the variations in irritability in the different experiments readily comparable the curves shown in Fig. 1 have been plotted. These are curves of irritability (reciprocal $\beta \times 10^4$) reduced to a percentage basis. In each experiment the average irritability for

[1] GRABFIELD and MARTIN: *loc. cit.*, p. 306.

TABLE I

Time P.M.	July 13–14, 1912		July 9–10, 1913				Sept. 6–7, 1913			
	Subject Bk.		Subject Bg.		Subject W.		Subject Bg.		Subject W.	
	β	recip β	β	recip β	β	recip β	β	recip β	β	recip β
7.30	61.9	161								
8.00			95.5	105	133	75	70.1	143	114.4	87
8.30	71.75	139								
9.00			73.5	136	126	79	58.3	171	121.6	82
9.30	85.6	117								
10.00			89	112	126	79				
10.30	88.8	112					77.8	129	143.5	70
11.00			81.8	122	127	79				
11.30	93.2	107					86.7	115	145.6	69
12.00	Sleep		77	130	151.6	66	Sleep		Sleep	
A.M. 12.30	79.5	126			Sleep					
1.00			89	112	134	75	97.1	103	150.9	66
1.30	Sleep				Sleep					
2.00			72.6	138	138	72	Sleep		Sleep	
2.30	71.3	140			Sleep					
3.00			78.5	127	133	75	91.4	109	145.6	69
3.30	Sleep				Sleep					
4.00			78.1	128	158	63	Sleep		Sleep	
4.30	97.7	102			Sleep					
5.00			83.9	119	148.5	67	104.4	96	143	70
5.30	Sleep				Sleep					
6.00			74.2	135	136.3	73			Sleep	
6.30	89.2	112								
7.00			72.5	138	145.7	68	68.5	146	133.7	75
7.30										
8.00										
8.30	86.6	115								

that experiment was drawn as a base line and the percentage variation from that average computed for each single irritability determination.[1] By plotting these latter data against the time intervals at which the determinations were made, the curves were constructed as shown.

Each experiment shows a point of low irritability near midnight. Exact coincidence in time of this point in different experiments is, of course, not to be expected. To our minds, however, the curves would be most instructive if the points of low irritability were superimposed. They were constructed, therefore, in that fashion. A short ordinate on each curve marks the position of midnight. The time at which the first sleep of the night began is indicated by the abbreviation Sl.

The time relation of the second point of low irritability to the first one is shown in a general way by an ordinate drawn to correspond with an interval of four hours from the first time of low irritability.

Significance of the Results. — We are not disposed to attempt to draw any far-reaching conclusions from the facts reported. So many factors undoubtedly are concerned in determining the condition of the nervous system at any time, that only after the accumulation of very numerous data will authoritative generalizations be justified. In one or two respects, however, our results seem to us significant. The two points of low irritability may perhaps be correlated with other well recognized physiological states occurring synchronously. Thus, the first low point corresponds in general with the period at which sleep ordinarily comes on, and may possibly be explained in terms of a raising of the nervous threshold accompanying the onset of the sleep taste. The second low point coincides fairly closely with the period of lowest body temperature, as determined by Jürgenson, Liebermeister, and others.[2]

Moreover, these points of low irritability are separated by about the same interval as was noted by Mönninghoff and Piesbergen [3]

[1] Grabfield and Martin: *loc. cit.*, p. 307.

[2] See Pembrey: Schäfer's textbook of physiology, Edinburgh and London, 1898, i, p. 799.

[3] Mönninghoff and Piesbergen: Zeitschrift für Biologie, 1883, xix, p. 114.

in their studies of the depth of sleep, as intervening between the periods of greatest sleep-intensity, and there is also a fair agreement in time between the periods of low irritability and those of great sleep-intensity. This coincidence may possibly signify that the rhythm which occurs in the human nervous system during the night is more or less independent of the state of sleeping or waking. Granting this as a valid possibility, the further assumption suggests itself, that the periods of deep sleep do not necessarily represent unusually great departures from the corresponding waking state, and need not therefore be exceptionally restful portions of the entire sleep interval. This assumption agrees with the common experience, voiced by Howell,[1] that short periods of deep sleep are not as effectual in restoring the nervous system as are longer periods of lighter sleep.

The experiment of July 9–10, 1913, (No. 2, Fig. 1), lends support to the suggestion that sleep, at least when interrupted at intervals as in this case, does not modify to any marked extent the state of the nervous system, judged by the sensory threshold. In this experiment one subject, W., slept during fully three-fourths of every hour from midnight to six in the morning. The other subject did not sleep at all. Yet the two curves are strikingly parallel. The parallelism of the curves is particularly interesting in view of the fact that the corresponding points are one hour apart.

A point to be emphasized in connection with the comparisons and suggestions made above is that our experiments did not include conditions which could be looked upon as representing extreme or even considerable fatigue. Our subjects had had no fatiguing experiences immediately previous to the experiments, nor were the experiments themselves specially wearying. Common experience shows that a single night of wakefulness after a day of ordinary activity may be endured without great discomfort and often without great desire for sleep. Our study had to do primarily with nocturnal variations of threshold in subjects as nearly normal as possible. The condition of the nervous system, both asleep and awake, during extreme fatigue, is a matter for further investigation.

[1] HOWELL: Textbook of physiology, 5th edition, Philadelphia, 1913, p. 255.

SUMMARY

Experiments on young adult male human beings carried on during nights of wakefulness or of interrupted sleep show that the irritability of the nervous system, as indicated by the sensory threshold for faradic stimulation, sinks during the early part of the evening to a low point near midnight; recovers somewhat during succeeding hours; and sinks again about four hours after the first low point to a second low point. After this low point there is recovery of irritability to the daytime level.

These variations in irritability are shown to correspond to variations in the depth of sleep as studied by Mönninghoff and Piesbergen. The suggestion is offered that both variations may be expressions of a deep-seated rhythm of the nervous system, more or less independent of the waking or sleeping state.

CONTRIBUTIONS TO THE PHYSIOLOGY OF THE STOMACH

XIII. THE VARIATIONS IN THE HUNGER CONTRACTIONS OF THE EMPTY STOMACH WITH AGE

By T. L. PATTERSON

[From the Hull Physiological Laboratory of the University of Chicago and the Physiological Laboratory of the University of Maryland]

THE experiments summarized in this report were undertaken at the suggestion of Professor Carlson to determine whether the activity of the empty stomach varies with the age of the animal. Some of Carlson's work on related problems seemed to indicate that the hunger contractions of the stomach decrease with the age of the animal, and the results of the following experiments confirm this idea. If the gastric hunger mechanism is closely correlated with the animal's actual need of food one would naturally think that the activity of a young animal's stomach would be much more marked than that of an aged animal, for healthy young animals are usually more active than older ones and this indicates a greater metabolic activity on the part of the organism, to say nothing of the additional requirements for growth. Apart from this correlation of gastric hunger activity with the food requirements of the animals at different ages, it is probable that the gastric hunger mechanism itself "grows old," parallel with the aging of the animal as a whole, as is the case with most of the organs of the body. As a rule, the increasing age of an organ is paralleled by decreasing activity of the organ. The stomach of an old animal may therefore exhibit less vigorous hunger contractions because of the actual age of the stomach itself, irrespective of correlations with bodily needs.

Method of Experimentation. — Four groups of dogs of different ages were selected; namely, a pup five to six months of age, a young adult, an adult, and an old adult. In all cases care was taken to choose only dogs in good condition and perfect health,

as far as could be judged by actions and external appearances. These dogs were operated on for gastric fistula according to the method described by Carlson[1] and as soon as the wound healed sufficiently, which usually required from five to seven days, the movements of the empty stomach were studied by Boldireff's method with the exception that a more delicate balloon was used which was connected with a chloroform manometer and used with a pressure of from three to six centimetres. The observations were made twenty-four hours after feeding, in order to assure an empty stomach. The animals were given at least one day or more of rest after each experiment so as to be in a perfectly normal condition when used again. During the taking of the records they were held in the lap, apparently without any appreciable discomfort for they nearly always slept through a large part of the experiment. In fact, they became so well trained after a few trials that when removed from the cages they would chase the experimenter from one room of the laboratory to another and watch for the first opportunity to jump into his lap in order to cuddle down and go to sleep. Five different series of records of the hunger movements of the empty stomach were obtained from each dog on five separate days, the continuous experimental periods ranging from two and a half to four and a half hours, respectively. This first series of dogs were then followed by a second similar series as controls.

In addition also to the two above series of dogs, a small pup five to six weeks of age was operated on for gastric fistula. This was on August 4, and three days later the wound had healed so that the first record of the stomach's movement was taken. This animal being so very small it was necessary of course to use a smaller balloon and also a different manometer. The balloon used was of the same delicacy as those used on the older dogs, but was only about one-third as large and connected with a water manometer with three to six centimetres' pressure. It was found impracticable to hold such a small animal in the lap so an armed office chair was selected and covered with a laboratory coat, the front of the chair seat being rather darkened and boxed in by raising the lower portion of the overlapping coat and attaching

[1] CARLSON: This journal, 1913, xxxii, p. 369.

it. Here the pup was placed and after a trial or two he became so well accustomed to his new environment that nothing suited him better than a good long nap there. No control was run on this young pup because no other pup of that age was available, but of the series of records obtained several were of longer duration than any taken on the other dogs, the longest one representing a continuous period of six and one-half hours, in which there was only one true rest period lasting two and one-half minutes (Fig. 1). This particular record was commenced eighteen

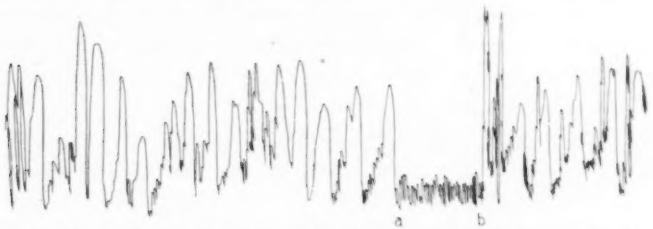


FIGURE 1. (One-half the original size.) Tracing from the empty stomach of a very young pup, five to six weeks of age, showing the very rapid contractions and the very short quiescence period, *a* to *b*, of two and one-half minutes' duration. Water manometer.

hours after the feeding of the animal. All the records were taken on a slowly moving drum revolving at the rate of about fifty minutes per revolution. The time for the contraction and quiescence periods was figured by means of a chronometer record.

RESULTS

The general character of the gastric hunger contractions in adult dogs has been reported by Carlson. After the introduction of the balloon into the stomach there is usually a short period of inhibition and then as the dog becomes quiet there is an increase in the tonus of the stomach. The strong hunger contractions gradually increase in amplitude and the pause between them becomes shorter and shorter until the period usually ends in very powerful and rapid contractions approaching incomplete tetanus. This is very evident in the older dogs and less so in the younger dogs, for the stronger contractions are going on practically all the time. Furthermore, the regularity of these movements is greatly

disturbed and also inhibited for a longer or shorter period depending on the disturbing influence, such as noise, fright, pain, anger, exciting influences, sight or smell of food, irritation such as around the fistula due to the presence of gastric juice, or by an unhealthy condition of the dog. In all the dogs studied the strong hunger contractions were usually preceded by restlessness as shown by the twitching of certain skeletal muscles, slight groaning, or stretching and waking from sleep, while sometimes these disturbances occurred in the upstroke of the curve, thus indicating that they are more or less disagreeable and painful to the animal. These effects appeared to be more magnified in the young animals than in the old, especially in the pups five to six weeks and five to six months of age, respectively.

The results summarized in Table I were computed from the tracings made from the different series of dogs and these figures in each case represent as nearly as possible the true time of activity and rest of the empty stomach, everything in the records of a doubtful character, or of an abnormal nature caused by disturbing influences, being entirely eliminated. The length of both the contraction and quiescence periods as observed by Boldireff seems on the whole to be considerably less than that shown in my series of old dogs (for doubtless he worked with old dogs). In fact, these two respective stomach periods seem to be much more variable in old dogs than in the young. My results on adult dogs are practically identical with those reported by Carlson. The differences between the results obtained by Boldireff and my own are probably due to the condition of the animals, the method of handling, and the method of registering the stomach contractions, for his dogs were forced by mechanical means to lie or stand in one position for six to twelve hours at a time, while mine were allowed to lie comfortably in the lap and sleep if they so desired. This forced position probably in part produced the brevity of the contraction periods. Boldireff's dogs also had other fistulae which would tend to make them more or less abnormal, perhaps interfering with the processes of digestion, while mine contained only the one fistula in the fundus portion of the stomach. A comparison of some of the records made from the different dogs may be had by a study of Figs. 1, 2, and 3.

TABLE I

SUMMARY OF OBSERVATIONS ON THE LENGTH OF THE CONTRACTION AND QUIESCENT PERIODS OF THE EMPTY STOMACH OF DOGS OF DIFFERENT AGES

First Series of Dogs				Controls		
Dogs	Sex	Length of contraction period	Length of quiescent period	Sex	Length of contraction period	Length of quiescent period
Old adult	♀	30 min. to 2 hr.	$1\frac{1}{6}$ to $3\frac{3}{5}$ hr.	♂	35 min. to $1\frac{3}{4}$ hr.	$1\frac{3}{5}$ to $4\frac{1}{6}$ hr.
Adult	♀	$1\frac{2}{3}$ to 3 hr.	$1\frac{1}{6}$ to 2 hr.	♀	$1\frac{1}{2}$ to 3 hr.	$1\frac{1}{2}$ to 2 hr.
Young adult	♀	$2\frac{3}{4}$ to $3\frac{3}{4}$ hr.	1 to $1_1^1{}_2$ hr.	♀	3 to $3\frac{3}{4}$ hr.	$1\frac{1}{4}$ to $1\frac{3}{4}$ hr.
Pup (age 5–6 mos.)	♂	3 to 4 hr.	5 to 10 min.	♀	3 to $4\frac{1}{3}$ hr.	5 to 10 min.
Young pup (age 5–6 wks.)	♂	$4\frac{1}{2}$ to $5\frac{3}{4}$ hr.	2.5 to 3.4 min.			

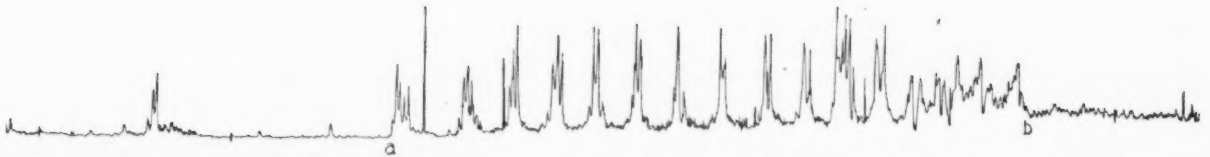


FIGURE 2. (One-third the original size.) Tracing from the empty stomach of an old dog showing a complete contraction period, *a* to *b*, of thirty minutes' duration. Chloroform manometer.

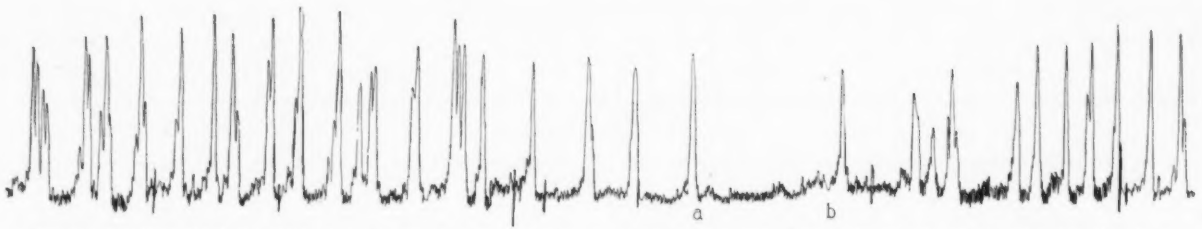


FIGURE 3. (One-third the original size.) Tracing from the empty stomach of a pup, five to six months of age, showing the short quiescence period, *a* to *b*, of six and twenty-five hundredths minutes' duration. Chloroform manometer.

As regards variation of stomach movements between dogs of different ages, the chief and practically the only constant difference was found in the length of the periods of contraction and the periods of quiescence. In all cases the periods of quiescence are the longest in old dogs, varying from one and one-sixth to four and one-sixth hours, and rapidly decreasing in length proportionately to age to two and one-half to three and four-tenths minutes in the very young pup of five to six weeks. Conversely the periods of contraction are the longest in the young dogs — for instance, in the very young pup the recorded periods run from four and one-half to five and two-thirds hours — and they rapidly decrease in length proportionately to age, in the old dogs from thirty minutes to two hours, thus showing that the stomach's activity is in direct proportion to the age of the animal.

The rapidity of the strong hunger contractions during the active periods appears on the whole to be greater in young animals than in old. The tonus of the stomach and also the strength of the contractions in young animals may be slightly higher, but they are subject to great variations. The decrease in the activity of the stomach as the animal approaches senility is probably an explanation in part at least for the more chronic gastric disturbances in the aged.

Summary

1. In healthy dogs the hunger contractions of the empty stomach decrease with age. This decrease appears to some extent in the tonus and in the rapidity of the hunger contractions, but is particularly marked in the duration of the periods of hunger activity and the intervening periods of quiescence of the stomach. On the whole the decrease in the gastric hunger activity is proportional to the advance in age. In very young dogs the hunger contractions of the empty stomach are practically continuous.

2. Two factors are probably involved in this variation of the gastric hunger contractions; namely: (1) the actual age of the gastric motor mechanism; (2) the correlation of the gastric hunger mechanism with the metabolic gradient or the need of food. The relative importance of these two factors must be determined by direct experiments.

AN EXPERIMENT TO PROVE THAT THE CILIA OF THE HUMAN NOSE WAFT TOWARD THE ANTERIOR NARES

By W. SOHIER BRYANT

THE author was so interested, from a clinical point of view, in the question of the direction in which the cilia of the nose waft that he conducted the following experiment: Fresh turbinal tissue from human turbinotomies was placed in isotonic saline solution at the body temperature and small pieces of rubber dam measuring 1. to 0.5 mm. were laid upon it. He observed that the rubber dam was moved *forward* with the adherent mucus at the rate of from one (1) to four (4) millimetres per hour.

This experiment was repeated on several occasions and conclusively proves what was theoretically anticipated, namely, that the cilia of the mucous membrane of the human nose waft toward the anterior nares and not toward the choanae.

From a theoretical point of view also, it would seem a priori that the cilia would cast the accumulated sediment from the inspired air out of the body in the most expeditious way, and the most expeditious way would be by the external nares. Also, the observation of collections of mucus containing dust and soot particles at the anterior nares suggests that the cilia waft in the direction of the anterior nares.

Especially noteworthy in this connection is the physiological convulsive explosion called "sneeze," a reflex act to clear the nose. The sneeze drives the contents of the nose from behind forward out of the anterior nares. If this explosion were against the direction of the cilia considerable traumatism would result to the delicate Schneiderian membrane.

In a careful search of the literature on this subject I was unable to find any statement that these cilia waft forward toward the anterior nares in man.

THE STATE OF THE VASOMOTOR CENTRE IN DIPHTHERIA INTOXICATION[1]

By W. T. PORTER and J. H. PRATT

[From the Laboratory of Comparative Physiology in the Harvard Medical School.]

Introduction

IN 1896 and 1899 Romberg and his students[2] published an influential experimental study on the nature of the circulatory disturbance in certain acute infectious diseases. They brought forward evidence which seemed to show that the collapse in experimental diphtheria and other infections which they produced in rabbits was due to paralysis of the vasomotor centre in the medulla oblongata. Subsequent investigators of this subject, Enriquez and Hallion,[3] Rolly,[4] von Stejskal,[5] Pässler and Rolly,[6] and Gottlieb,[7] accepted Romberg's conclusions, although Enriquez and Hallion, von Stejskal, and Gottlieb were of opinion that the heart also was directly injured.

In all these investigations, the opinion that the vasomotor centre is gravely affected or "paralyzed" is based upon the failure of the observer to obtain any rise in blood pressure in asphyxia, upon stimulation of the nasal mucous membrane, or on stimulation of the sciatic nerve. The testimony is entirely negative and is open to the objection inseparable from negative experimental results,

[1] Aided by a grant from the Proctor Fund for the study of chronic diseases.

[2] Pässler and Romberg: Verhandlungen des xiv Congresses für innere Medicin, Wiesbaden, 1896, p. 256. Romberg, Pässler, Bruhns, and Miller: Deutsches Archiv für klinische Medicin, 1899, lxiv, p. 652.

[3] Enriquez and Hallion: Archives de physiologie, 1898, p. 393.

[4] Rolly: Archiv für experimentelle Pathologie und Pharmakologie, 1899, xlii, p. 283.

[5] Von Stejskal: Zeitschrift für klinische Medicin, 1902, xliv, p. 367.

[6] Pässler and Rolly: Deutsches Archiv für klinische Medicin, 1903, lxxvii, p. 96.

[7] Gottlieb: Medizinische Klinik, 1905, i, p. 617.

namely, that the failure to obtain a reaction may be due to imperfections in technique.

We purpose in the present research to bring forward a positive, not a negative result.

Method

In this research diphtheria toxin was injected into an ear vein of rabbits. Some hours before death would probably have taken place, the state of the vasomotor centre was determined by measuring the reflex change in blood pressure obtained by stimulating the depressor and the sciatic nerves.

The results thus obtained were confirmed by measurements made upon an animal which had died from the disease and in which the circulation had been revived.

The details of the method are as follows.

The diphtheria toxin was obtained from the antitoxin and vaccine laboratory of the Massachusetts State Board of Health through Professor Theobald Smith and Mr. Herbert R. Brown, to whose courtesy we are much indebted. With the toxin first used, 0.005 c.c. was found to kill guinea pigs of 250 to 300 grams weight in 72 hours, with a variation of about 3 hours. To 2 c.c. of the toxin were added 8 c.c. normal saline solution (NaCl .008). Of this first dilution, 2 c.c. were further diluted by adding 198 c.c. normal saline solution. Thus 1 c.c. of the final mixture, called Solution II, contained .002 c.c. toxin. Of Solution II, one cubic centimetre per 500 grams of body weight was injected into an ear vein, usually the marginal vein. In a few experiments, a somewhat larger amount was used.

The question now arises whether the rabbits studied were gravely ill of the disease when the vasomotor reactions were measured. It would be expected that the hour of approaching death might be predicted (1) by the character of the symptoms and (2) by the time required for a measured quantity of toxin to kill an animal of given weight.

The symptoms unfortunately are of uncertain value. The rabbit refuses food and is apathetic, but there are frequently no further definite signs until just before death takes place. Even when the animal is no longer able to keep his erect posture or

hold up his head, but lies on his side, death may be postponed for several hours or it may occur in a few minutes. In short, prediction of the hour of death by observations of the symptoms is difficult and unsatisfactory.

There remains prediction based on the amount of toxin injected. Our observations on this subject are given in Table I.

TABLE I

THE NUMBER OF HOURS DURING WHICH RABBITS SURVIVED AFTER RECEIVING THE DIPHTHERIA TOXIN

Rabbit No.	Weight in grams	c.c. Toxin per kilo weight	Date of injection	Hours of life	Remarks
			1912		
14	1950	.006	12 m. Apr. 11	30 to 43	Died during night of Apr. 12.
16	2350	.006	1.20 p.m. Apr. 21	5 to 19	Found dead, Apr. 22, 9.30 A.M.
18	1950	.005	12.35 p.m. Apr. 23	6 to 18	Found dead on morning of Apr. 24
21	1500	.004	4.15 p.m. May 25	46	
			1914		
29	2150	.003	Jan. 13	31 to 36	The toxin employed on Nos. 29–42 was such that .0035 c.c. killed guinea pigs of 250 to 300 grams in 60 hours.
30	2025	.003	Jan. 13	55 to 63	
31	1700	.004	Jan. 13	34	
32	1500	.004	Jan. 13	46	
33	1000	.004	Jan. 13	40 to 46	
34	1300	.003	Jan. 15	94	
35	2000	.003	Jan. 15	56 to 57	
36	1750	.003	Jan. 15	92	
37	1350	.004	Jan. 18	41 to 44	
38	1550	.004	Jan. 18	41 to 42	
39	1400	.004	Jan. 18	50	
40	1550	.004	Jan. 18	37 to 38	
41	1400	.004	Jan. 18	29 to 30	
42	1400	.004	Jan. 18	34 to 35	

In this table the first four cases are those of rabbits in which death took place before the vasomotor reflexes could be measured. The remaining fourteen animals were injected for the purpose of determining how long rabbits would live after receiving toxin in amounts comparable to the amounts given the rabbits in which we measured the vasomotor reflexes. It appears that the first four animals in Table I died in 46 hours or less, while the average duration of life in the fourteen rabbits specially investigated was 50 hours.

In Table II are given data concerning the rabbits in which the vasomotor reflexes were measured. It will be noted that the measurements were begun as an average 39 hours after the injection of the toxin.

We have therefore the following premises. It is alleged that the vasomotor apparatus is deeply affected in fatal cases of diphtheria intoxication. Observations on fourteen rabbits show that death took place as an average in 50 hours. In ten other rabbits, similarly poisoned, the vasomotor reflexes were measured as an average 39 hours after injection. It seems reasonable to expect that at this time, 39 hours after injection and but 11 hours before probable death, the vasomotor apparatus would have been impaired, had its impairment been an important feature of the disease.

The Measurement of the Vasomotor Reflex. — It is known that curare and ether both affect the changes of blood pressure obtained by stimulating the afferent vasomotor nerves. Regarding curare, it is to be noted that a decisive number of our observations on the depressor nerve were made without this drug. The reflex from the sciatic nerve must of course be obtained from a curarized animal. In all such, the curare was injected in dilute solution slowly through the external jugular vein. The reflexes were measured through a period longer than that during which the curare might have caused a significant error in the readings.

The ether was given very cautiously, a few whiffs from time to time, in such a way as not to affect perceptibly the blood pressure during the observations.

Where artificial respiration was employed, the quantity of air used was the least that would keep the blood properly oxygenated.

Great care was used in the preparation and subsequent handling of the nerves. The stimulating current was from an inductorium supplied by constant Daniell cells and the current strength was that distinctly perceptible to the operator's tongue.

The mercury manometer was usually employed, but some blood pressures were recorded with a membrane manometer.

Blood Pressure at the Beginning of Stimulation.—Information regarding the state of the animal may be obtained from Table II,

TABLE II

BLOOD PRESSURE WHEN STIMULATION OF AFFERENT NERVES WAS BEGUN

Rabbit No.	c.c. Toxin per kilo weight	Hours after inoculation	Blood pressure	Remarks
			mm. Hg	
4	.004	43	58	
6	.004	42	80	
7	.006	16 [1]	66	
8	.004	42	80	
9	.004	41	92	
10	.005	41	50	Low blood pressure probably due to curare and exposure of splanchnic nerves.
11	.004	41	46	Curare
12	.004	42	47	"
20	.004	39	97	"
21	.004	41	42	"

[1] This rabbit received an unusually large dose of toxin.

which shows the blood pressure at the time the stimulation of the afferent nerves was begun. The average blood pressure in the ten rabbits was 66 mm. Hg. In the five in which no curare was given, the blood pressure averaged 75 mm. Hg. It is clear that in these animals the blood pressure was not seriously affected. If it be urged that the blood pressure is seriously affected only in the very last hours of the disease, we present this additional observation upon a rabbit in which death was imminent.

Experiment January 19, 1914. — Rabbit No. 34, weighing 1300 grams, had received through the ear vein .003 c.c. diphtheria toxin at 5.10 P.M., January 15. On January 17, food was refused, but at 10 A.M., January 19, it was noted that the rabbit did not seem very ill. At 3 P.M., however, he was unable to stand, and at 3.30 he was flaccid and insensible and obviously near death. At that hour, the depressor nerve was exposed and a cannula placed in the carotid artery. The rabbit was wholly insensitive to the operation, so that no anaesthetic was necessary. The heart beats were so feeble that they scarcely lifted the lever of a sensitive membrane manometer, quite undamped. The blood pressure was 80 mm. Hg and fell to 50 mm. on stimulation of the depressor nerve, an absolute fall of 30 mm. (37.5 per cent). After stimulation, the blood pressure rose quickly to its former level.

Thus in our observations the blood pressure was not seriously lowered even in the last stages of the disease.[1]

The Depressor vs. the Sciatic Nerve as an Index to the State of the Vasomotor Cells. — The depressor nerve contains only afferent vasomotor fibres; the sciatic contains fibres of widely different functions. The depressor impulses reach the vasomotor centre directly; the sciatic impulses must pass first through the spinal cord, where the conducting apparatus is subject to influences not found in the case of the depressor nerve. The depressor reflex can be measured without administering a drug, whereas the sciatic reflex can be measured only after the administration of curare, a poison the effects of which cannot positively be limited to the motor end-plates. Finally, the depressor reflex can be measured without artificial respiration, but the sciatic reflex requires artificial respiration, the unskilful use of which introduces serious errors into measurements of blood pressure.

All these are excellent reasons for preferring the depressor nerve as the indicator of the condition of the bulbar vasomotor cells.

In this research the results gained with the depressor were confirmed by stimulation of the sciatic nerve.

[1] It is equally true that unless care and skill be employed, the blood pressure will fall rapidly under the operative procedure.

The Sciatic Vasomotor Reflex in Diphtheria Intoxication

For the reasons stated in the preceding paragraph we have used in this investigation chiefly the depressor nerve, but we have stimulated the sciatic nerve often enough to show that in diphtheria intoxication the sciatic reflex does not indicate a noteworthy change in the power of the vasomotor centre. The average rise from stimulation of the sciatic nerve was 33 per cent while the average fall from stimulation of the depressor nerve, as shall presently be shown, was 36 per cent. The observations on the sciatic reflex are given in Table III, showing 18 stimulations in 5 rabbits.

TABLE III

The Absolute and Percentile Change in Blood Pressure upon Stimulation of the Central End of the Sciatic Nerve at Different Levels

Beginning level of blood pressure	Number of observations	Average absolute rise	Average percentile rise
mm. Hg		mm. Hg	%
71 to 80	1	18	24
61 to 70	2	38	36
51 to 60	1	8	22
41 to 50	1	26	57
31 to 40	4	10	26
21 to 30	3	7	29
11 to 20	6	7	37

The Depressor Vasomotor Reflex in Diphtheria Intoxication

The measurements of the depressor reflex may be divided into two series. The first consists of 23 observations on ten rabbits, between March 29, 1912, and May 25, 1912. The second series contains the rabbits of January 19 and January 20, 1914.

First Series. — The observations of the first series appear in

Table IV. It is seen that in measurements made at initial blood pressures between 30 and 100 mm. Hg the average fall on stimu-

TABLE IV

THE ABSOLUTE AND THE PERCENTILE CHANGE IN BLOOD PRESSURE UPON STIMULATION OF THE CENTRAL END OF THE DEPRESSOR NERVE AT DIFFERENT LEVELS

Initial level of blood pressure	Number of observations	Average absolute fall	Average percentile fall
mm. Hg		mm. Hg	%
91 to 100	1	19	20
81 to 90	6	33	40
71 to 80	2	38	48
61 to 70	4	23	35
51 to 60	2	20	38
41 to 50	4	19	38
31 to 40	4	13	35

lation of the depressor nerve was 36 per cent ;[1] a fall as great or greater than that obtained in animals not poisoned with diphtheria toxin.[2]

The conclusion is inevitable that in rabbits examined as an average 39 hours after receiving a lethal dose and 11 hours before their probable death from diphtheria toxin the vasomotor centre is substantially normal.

It is highly probable that the vasomotor centre would at this time (39 hours after the lethal dose was administered) have been impaired were diphtheria toxin specifically injurious to the vasomotor cells.

Second Series. — Conclusive evidence against the hypothesis that the vasomotor centre is "paralyzed" in diphtheria intoxication is afforded by the experiments of January 19 and January 20. The

[1] In 262 observations on unpoisoned animals made by W. T. Porter the average depressor fall was 33 per cent.

[2] W. T. PORTER: This journal, 1907, xx, p. 403.

protocol of the first of these experiments, given on page 436, clearly indicates that the rabbit, "flaccid and insensible," was about to die. In the experiment of January 20, systemic death had actually taken place, the respiration had ceased beyond recall, the heart had stopped, the arteries were empty, but the vasomotor cells were still intact and the heart was made to beat again long enough for the vasomotor reflex to be measured. Following is the protocol.

Experiment January 20, 1914. — A rabbit weighing 1400 grams received in the ear vein .004 c.c. diphtheria toxin at 1.05 P.M, January 18. The morning of January 20 the rabbit seemed listless. It was placed on a table and observed continuously from 9 A.M. As the day wore on, the rabbit could not hold up the head, nor regain his feet when laid upon one side. Finally,

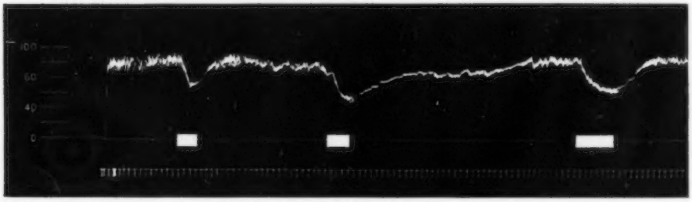


FIGURE 1. From an animal dead of diphtheria toxin, but with surviving vasomotor cells and resuscitated circulation. The upper line shows carotid blood pressure recorded with a membrane manometer. The graduation scale in mm. Hg is seen at the left. The middle line records the atmospheric pressure and the stimulation of the depressor nerve. The lower line gives time in 5-second intervals.

about 3.15 P.M., he lay prone, the head stretched on the table, and the respiration feeble and labored. At 3.30 he seemed so near death, that he was placed on the operating board. Death at once followed; there was no corneal reflex, no respiration, no heart beat, the carotid artery seemed empty, and the rectal temperature was 32° C. The rabbit was completely insensitive. It was quickly tracheotomized and artificial respiration was established. Warm normal saline solution was injected into the external jugular vein. The heart began to beat, though feebly, scarcely raising the writing point of a membrane manometer, completely undamped. The carotid pressure rose to about 80 mm. Hg. Both vagi were now cut and the depressor nerve was stimulated; three of the stimulations are shown in Fig. 1; in

these three the pressure fell on stimulation from 80, 70, and 72 mm. Hg to 52, 40, and 45 mm., respectively; an absolute fall of 28, 30, and 27 mm. Hg, and a percentile fall of 35, 43, and 38.

Thus, a normal reaction from the vasomotor centre was obtained on stimulating the depressor nerve in an animal that had died of diphtheria intoxication.

Conclusion

The experimental evidence proves that the vasomotor centre is not impaired in fatal diphtheria intoxication.

PROCEEDINGS OF THE AMERICAN PHYSIOLOGICAL SOCIETY

TWENTY-SIXTH ANNUAL MEETING

PHILADELPHIA, DECEMBER 29, 30, 31, 1913

PROCEEDINGS OF THE AMERICAN
PHYSIOLOGICAL SOCIETY

THE CONTOUR OF THE INTRAVENTRICULAR AND THE PULMONARY ARTERIAL PRESSURE CURVES BY TWO NEW OPTICALLY RECORDING MANOMETERS

By CARL J. WIGGERS

A STUDY of the pressure variations in the right ventricle and the pulmonary artery was undertaken, not merely to establish the normal pressure curves, but also to determine what factors were capable of modifying their contour. In such an analysis it was hoped to find the key for interpreting and explaining the changes that the acts of respiration cause in the pulmonary and systemic blood pressures.

In order to study these changes with instruments combining a high vibration frequency and great sensitiveness with convenience in application and operation two new forms of optically recording manometers were shown, the details of which will be described in other communications to appear in this Journal.

Results: The pressure curve in the right ventricle obtained under normal conditions of venous and pulmonary arterial pressures may be divided into (*a*) an auricular period, (*b*) an isometric period, (*c*) an ejection period, and (*d*) a relaxation period. The steepness of the isometric curve (i.e., while the tricuspid and semilunar valves remain closed) is modified by (1) auricular pressures and (2) vigor of cardiac contraction. Its height, regulated by the diastolic arterial pressure previous to opening of the semilunars, is modified by (1) the auricular pressure and (2) changes in the resistance within the pulmonary circuit. Comparison

shows that the curves obtained after compressing the lung vessels modify the height of the isometric period in a manner directly opposite to lung inflation (natural or artificial). This leads to the inference, which is substantiated by the change in the pulmonary arterial pressure curve, that during lung inflation the pulmonary vessels are dilated.

The curve of the ejection period, which follows opening of the semilunar valves, corresponds in shape to the pressure curve within the pulmonary artery. It rises, reaches its summit, and then declines until the semilunar valves close. The rapidity of the rise and the lapse of time before the summit is reached determine whether the curve, as a whole, when written on a more slowly moving film, gives the appearance of a rounded or flattened top. Since this is determined by the pulmonary arterial pressure, it follows that the factors above mentioned may decidedly affect the contour of the pressure curve.

A negative extra cardial pressure, when great, decreases the steepness and height of the isometric contraction, both by impeding the diastole and diminishing the initial tension for ventricular contraction. So far no evidence has been obtained, however, that variations such as normally occur in the unopened chest affect the intraventricular pressure curve.

THE DIALYSIS OF THE NORMAL CIRCULATING BLOOD

By C. L. v. HESS and H. McGUIGAN

A simple method of dialyzing the normal circulating blood was devised primarily to determine the condition of the sugar in the blood. It was intended so far as possible to avoid the decomposition of the form elements and the possible breakdown of any sugar compound if such existed. Many other problems may be attacked by the method.

The method consists in attaching a dialyzing apparatus of artificial blood vessels composed of collodion, between the carotid artery and external jugular vein. A connection may be made

between any other artery and vein. No anticoagulant was used. Clotting in the dialyzer was prevented by flushing out the apparatus about every ten minutes. This is easily accomplished if three-way cannulas are used to connect the artery and vein with the dialyzer. The diagram shows the dialyzer.

The authors were unaware of the priority of Abel in this field. The method must be looked upon as a modification of his. The main difference is that we strenuously avoided the use of an anticoagulant while he used hirudin with great liberality. This allowed him to use a more complicated apparatus and a greatly increased dialyzing surface.

The method shows that most of the sugar, perhaps all, is in the free state. Phloridzin does not increase the rate of dialysis, even when the urine contains an abundance of sugar. In one trial diastasé was found free in the dialyzate, though in this case we did not work aseptically. Hexamethylenamin is not decomposed in the circulating blood.

THE CONDITION OF THE BLOOD IN HEMOPHILIA

By W. H. HOWELL

The paper gave the results of the examination of the blood of two boys presenting a typical history of congenital hemophilia. The cases were examined repeatedly over a period of a year.

Coagulation Time. — The blood was taken by venepuncture and 2 c.c. were placed in clean weighing tubes to clot. As determined by this method the coagulation time of normal blood varied between twenty and forty minutes, that of the hemophilic blood between four and five hours.

Antithrombin. — The antithrombin was estimated in the clear plasma of the oxalated blood after heating to 60° C. to destroy the fibrinogen and prothrombin. The antithrombin value was estimated by determining the delay in clotting caused by this heated plasma when added to known mixtures of fibrinogen and thrombin. The results of fourteen examinations indicated that the antithrombin in hemophilic blood is present in amounts equal to, or, in some cases, slightly in excess of that shown by normal blood.

Prothrombin. — The tests used to determine this factor indicated that the available prothrombin in hemophilic blood is markedly less than in normal blood. The author concluded that the characteristic delay in coagulation in hemophilic blood is caused by this diminution in prothrombin. It was stated that the blood of dogs may be brought into a hemophilic condition, as defined above, by the injection of large doses of epinephrin.

FARADIC STIMULI: — A PHYSICAL AND PHYSIOLOGICAL STUDY

By JOSEPH ERLANGER and WALTER E. GARREY

The form and duration of induction shocks yielded by coils of the Du Bois-Reymond type, as determined by the string galvanometer and controlled by various physical and physiological means, while fairly constant for any one coil, vary considerably in the case of different coils. The stimulating value of the shocks is dependent entirely upon their ascending limbs and obeys the Du Bois-Reymond law. The decline of potential, even when it is made to take place instantaneously, does not seem to affect the stimulating value of the shocks. The duration of the shocks is much greater than the figures given in physiological literature, and this duration of the unmodified shocks may be greatly increased by foreshortening (short-circuiting) the shock. A make shock foreshortened to its crest may have a lower thresh-

old amplitude than the full break, and occasionally the threshold of the former, as determined by the position of the secondary coil, may be lower than that of the latter. Increasing the strength of the shocks increases perceptibly their duration, certainly in the phase beyond the crest. Strong shocks seem to be relatively more efficient physiologically than weak shocks.

When the rate of interruption of the primary is progressively increased the make and break shocks soon begin to overlap and to reduce mutually their amplitudes of potential, the break shock first being affected. Therefore, beyond a relatively slow rate of interruption, a rate that is determined primarily by the duration of the make shock, the threshold stimulating value of interrupted currents decreases as the rate increases. When at these rates the attempt is made to short-circuit out the make, the break shock is still further reduced in amplitude and the foreshortened make that always results may acquire a higher stimulating value than the break, and so reverse the stimulating pole.

A METHOD OF OBTAINING SUCCESSIVE CONTRAST OF THE SENSATIONS OF HUNGER AND APPETITE

By A. J. CARLSON

The experiment consists in swallowing a rubber balloon with rubber tubing attachment for recording the gastric hunger contractions, and a second rubber tube for the introduction of liquids or semisolids into the stomach without coming in contact with the mouth and the oesophagus.

At the height of a hunger contraction as shown by the recording manometer and by the intensity of the hunger sensation, cold water, beer, weak acids, or weak alcohol is introduced into the stomach by means of the second tube. These substances cause a temporary inhibition of the hunger contractions and hence abolish the hunger sensation; but the stimulation of the gastric mucosa by these substances gives rise to a sensation that appears to be identical with the sensation of appetite. When

the two sensations are compared by this device for placing them in successive contrast, they are plainly of different orders and not different degrees of the same kind of sensation.

The hunger sensation is essentially of an *unpleasant character* and when intense it is distinctly painful (protopatic pain). The appetite sensation induced by the stimulation of the normal gastric mucosa is essentially of a *pleasant character* and never under any circumstances painful.

A SUMMARY OF WORK ACCOMPLISHED WITH A RESPIRATION CALORIMETER IN BELLEVUE HOSPITAL

By EUGENE F. DuBOIS

The new respiration calorimeter of the Russell Sage Institute of Pathology resembles Benedict's bed calorimeter in Boston. Electric and alcohol checks have shown that the instrument can measure heat within 1.0%, oxygen within 0.34%, carbon dioxide within 0.28%, and water within 2.98%. The average respiratory quotient for alcohol has been 0.6670 instead of the theoretical quotient of 0.6667. In a total of 66 experiments on patients with various diseases the methods of direct and indirect calorimetry have agreed within 5% in two-thirds of the cases and within 3.5% in the total measurement of over 15,000 calories.

The average heat production of normal controls is 34.4 calories per hour per square metre of body surface. Working with Dr. Warren Coleman the metabolism of typhoid patients has been studied and it has been found that at the height of the fever the heat production is 30–50% above the normal average. At this stage of the disease meals containing 100 gr. of glucose or 10–11 gr. of nitrogen show little or no specific dynamic action although the same meals cause a rise of 10–15% in heat production in convalescence. It has been found also that the water elimination averages 33% higher in fever than in convalescence.

ON THE RAPID DISAPPEARANCE FROM THE BLOOD OF LARGE QUANTITIES OF DEXTROSE INJECTED INTRAVENOUSLY

By I. S. KLEINER and S. J. MELTZER

When large quantities of dextrose (4 gr. per kg. in a 20% solution) are introduced intravenously into dogs, the dextrose rapidly disappears from the blood. On an average 97% is lost from the blood in one and one-half hours. Of this, an average of 53% is found in the urine and 44% remains to be accounted for. With the kidneys ligated the amount of dextrose not accounted for is increased by about the amount which would have been in the urine if the renal function had been present, i.e., nearly all has disappeared from the blood. To exclude the liver and the other abdominal organs which may be concerned in decomposing or storing up sugar, in nine experiments the aorta and vena cava were tied near the diaphragm; in some cases also the thoracic duct was ligated and the thyroid glands removed. In the course of about an hour an average of about 84% had disappeared from the blood. It is therefore possible that the liver or some other abdominal organ is responsible for the disappearance of a small fraction of the dextrose in the experiments preceding this series.

In order to exclude the actual utilization of dextrose by the living tissues we next injected the sugar into dead animals. It was found that the dextrose leaves the blood quite rapidly, although not as quickly or as completely as in the living animal. In five experiments an average of 52.4% left the blood in a short time. Analysis of muscle tissue at the beginning and end of the experiment showed increases in carbohydrates calculated to be sufficient to account for the discrepancy. A similar result was obtained with dead animals having the aorta and vena cava tied.

In the muscle of the living animal there can also be found a large proportion of the dextrose lost from the blood, but sufficient work has not yet been done to determine whether any fraction undergoes decomposition or condensation.

Our general conclusion is that the disappearance of injected

dextrose is accomplished largely by passage into adjacent tissues, particularly the muscles. Physical factors alone are concerned in this process in the experiments on dead animals and it is quite probable that in the living animal vital factors play a less important rôle in this matter than has been ascribed to them by some investigators.

THE RELATIVE SYSTOLIC DISCHARGES OF THE RIGHT AND LEFT VENTRICLES AND THEIR BEARING ON PULMONARY DEPLETION AND CONGESTION

By Y. HENDERSON and A. L. PRINCE

In the excised cat's heart under coronary perfusion graphic records of the stroke of the right and left ventricles were obtained under various diastolic distending pressures.

The principal part of the apparatus connected with the heart consisted of two glass cylinders. In the lower end of each a brass cannula of suitable length and bore was held by means of a perforated rubber stopper. One of the cannulas was introduced into the left ventricle through one of the severed pulmonary veins, the other into the right ventricle through the superior vena cava. The closure of the mitral and tricuspid valves about the cannulas prevented regurgitation into the auricles. The diastolic distending pressure in either ventricle could be varied by the addition or removal of fluid in the cylinders. The oscillations of the fluid column in the cylinders, representing the ventricular stroke, was recorded by air transmission. The perfusion fluid consisted of equal parts of defibrinated sheep's blood and Locke's solution. The same mixture was used in the pressure chambers. All pressures mentioned subsequently refer to the diastolic distending pressure in millimetres of saline.

Three groups of experiments are presented. In the first, the right ventricular pressure was maintained at 50 mm. and that in the left was gradually raised from 0 to 210 mm; in the second the pressure was progressively and simultaneously increased in both ventricles from 0 to 170 mm.; and in the third the pressure

in the right ventricle was gradually increased, the left ventricular pressure remaining constant.

It was found that the right ventricle attains its maximum efficiency at 50 mm., pressures above 70 mm. causing a progressive decrease in the amplitude of its stroke. The stroke of the left ventricle at pressures below 50 mm. is always smaller than that of the right. Above 50 mm. the left ventricular output increases gradually, being equal to that of the right at 50 to 70 mm., and reaching its maximum at about 170 mm. With diastolic pressures of 50–70 mm. in both ventricles, the respective strokes are in equilibrium.

These observations serve as a basis for the conclusion that the pulmonary volume may be regulated in great part by the relative efficiency of the two ventricles. In life pulmonary depletion would be prevented by the inefficiency of the left ventricle at low diastolic distending pressures. Above 70 mm. the stroke of the left ventricle is always greater than that of the right at any pressure. Pulmonary congestion is thus normally prevented, as any increase in the pulmonary blood volume leads to a rise in left auricular pressure and thus induces an increased activity on the part of the left heart, by which the excess blood is pumped out of the lungs until pressure and volume are again normal.

THE EFFECT OF STRYCHNIN ON REFLEX THRESHOLDS

By E. L. PORTER

The experiments were performed on cats made spinal by cutting the cord in the neck and pithing the brain. A Sherrington electrode was placed on the tibial nerve and reflex movements elicited by single break shocks applied to its central end. At frequent intervals the thresholds of the flexion reflex, of the crossed-extension reflex, and of reflex extension of the fore-limb were determined by Martin's method.

Strychnin sulphate in 0.1 mg. doses was injected into the jugular vein at intervals of 2 to 10 minutes until the animal

exhibited violent convulsions. Before the injection the flexion threshold had usually a value of between 2 and 10 Z units. The crossed-extension threshold varied more widely, ranging from 5 to 300 Z units, and extension of the fore-limb could not be elicited by any strength of stimulus. In about one out of three animals after injection it was found impossible to demonstrate any lowering of the flexion threshold, although the thresholds for crossed-extension and for extension of the fore-limb dropped to within 2 Z units, or less, of the flexion threshold. In the remainder of the animals there was the same lowering of the thresholds for crossed-extension and extension of the fore-limb, and in addition a lowering of the flexion threshold of from 8 to 50 per cent.

THE ACCELERATION OF THE HEART IN EXERCISE

By H. S. GASSER and W. J. MEEK

A study was made of the parts played by the various mechanisms which have been described as producing an acceleration of the heart in the accelerations occurring in exercise. The experiments were done on dogs and the exercise consisted in running for two minutes. The reaction of the heart of the normal animal was compared with that occurring after one or more mechanisms had been removed.

After removal of the stellate ganglia no significant change was found in the actual acceleration in beats per minute. After vagotomy the acceleration was much impaired if two or three days were allowed to elapse for the accommodation of the respiration. After vagotomy and removal of the accelerators the findings were similar to those observed after vagotomy alone. If the extrinsic nerves of the heart were cut and the adrenals removed, neither exercise, asphyxia, nor anaesthesia produced any appreciable acceleration of the heart, although large accelerations were obtained before the extirpation of the adrenals. Acceleration is also possible over the accelerator innervation of the heart alone as it occurs after the vagi are cut and the adrenals removed. The

residual acceleration after adrenalectomy and cutting of the extrinsic cardiac nerves practically corresponds to that observed by Martin and others as occurring in the isolated mammalian heart for similar rises of temperature.

We conclude from our experiments that the acceleration of the heart in exercise is due mainly to inhibition of the cardio-inhibitory centre. This is aided especially in the more extreme conditions by the activity of the accelerator mechanism and the secretion of the adrenals. Temperature is a factor only as it affects the heart directly and does not depend on the stimulation of a reflex arc arising in and ending in the heart.

SOME MUTUAL RELATIONS OF OXALATES, SALTS OF MAGNESIUM AND CALCIUM; THEIR CONCURRENT AND ANTAGONISTIC ACTIONS

By F. L. GATES and S. J. MELTZER

At the October meeting of the Society for Experimental Biology and Medicine we reported our experiments on the combined action of sodium oxalate and magnesium sulphate on rabbits. We found that when a dose of 0.2 gm. of sodium oxalate is given subcutaneously on one side, and 0.8 gm. of magnesium sulphate is given on the other side, the animal sinks into deep anaesthesia and paralysis, equal to that produced by a dose of magnesium sulphate twice that given in the present instance. There is this difference, however, that the deep anaesthesia lasts a good deal longer than in the case of the double dose of magnesium alone. These experiments were undertaken on the basis of the well-known observations of Meltzer and Auer, that an injection of a calcium salt counteracts promptly a great part of the anaesthetic effect of magnesium, which seems to indicate that the normal conscious state depends upon the proper relation of magnesium to calcium in the fluids of the animal body. From this it would seem to follow that the same degree of anaesthesia could be produced either by an increase of magnesium or by a decrease of calcium. Since oxalates precipitate calcium we antic-

ipated that an injection of oxalate, with an inefficient dose of magnesium sulphate, would produce a deep anaesthesia equal to that from a much larger dose of magnesium sulphate alone.

Later we made observations upon the awakening effect of calcium in cases of deep anaesthesia produced by sodium oxalate plus magnesium sulphate. Intravenous injections of calcium chloride solutions are as strikingly efficient in these cases as in the deep states of anaesthesia produced by magnesium sulphate. In a minute or less after the beginning of the calcium injection the animal rouses, turns over, and sits up.

We have studied also the fatal effects of sodium oxalate given by intramuscular injection and the possibly favorable effect of the additional injection of magnesium sulphate or calcium chloride. Some of our results are as follows:

In 10 rabbits 0.2 gm. of sodium oxalate proved to be fatal in every case and the average duration of life was 30 minutes. All of the 10 rabbits which received 0.2 gm. of sodium oxalate intramuscularly, followed by one or more intravenous injections of calcium and sodium chloride, died, but the duration of life was 87 minutes. Of 10 rabbits which received 0.2 gm. of sodium oxalate and 0.4 gm. of magnesium sulphate, 4 remained alive, and the average duration of life in the six fatal cases was 137 minutes. Of 10 rabbits which received 0.2 gm. of sodium oxalate, 0.4 gm. of magnesium sulphate, and later 10 c.c. of a mixture of calcium and sodium chloride, 4 remained alive and the average duration of life in the six fatal cases amounted to 176 minutes.

THE OSMOTIC PROPERTIES OF CLAM'S MUSCLE

By E. B. MEIGS

The vitreous portion of the adductor muscle of the clam (*Venus mercenaria*) contains only 0.3% of chlorine, while the "clam-juice," by which the muscle is surrounded during the life of the animal, contains 1.6%. When the muscle is immersed for a day or more in sea water, double strength sea water, or 30% saccharose solution, the concentration of crystalloid in the muscle

rises to about half that of the surrounding solution, although the muscle remains alive throughout the period of its immersion. The muscle shows no tendency to lose weight in double strength sea water or 10% sodium chloride solution.

Experiments on the mantle, by which the adductor muscles are covered during the life of the clam, show that this tissue is nearly if not quite impermeable to sodium chloride.

There is, therefore, much reason to believe that the individual fibres of the clam's adductor muscle are not surrounded by semi-permeable membranes.

AN IMPROVED FORM OF APPARATUS FOR PERFUSION OF THE EXCISED MAMMALIAN HEART

By M. DRESBACH

The principal feature of the apparatus is a four-way stopcock which permits of the use of four different perfusion fluids in a single experiment, transition from one fluid to another being easily and quickly made without changing the pressure or temperature conditions under which the perfusion is being carried on. The stopcock is situated at the bottom of a cylindrical water bath, heated by a resistance coil and serving to bring the fluids to the desired temperature. A second bath raises the fluids to approximately the right temperature before they enter the main bath. The outlet of the stopcock, just below which the heart is suspended, contains a thermometer and connection for a manometer, which measure, at a point one inch above the aortic cannula, the temperature and pressure of the fluid being perfused. The capacity of the outlet tube is small; only one cubic centimetre of fluid must be displaced when one fluid is substituted for another. The side tube going to the manometer can be joined with a fifth fluid, which can be perfused at any desired temperature or pressure. The fluids are driven through the system by compressed air or oxygen. A fairly constant pressure can be obtained by making use of the principle of Hero's fountain.

The advantages of the apparatus are: simplicity of construc-

tion; convenience of operation; provision for use of at least five different solutions in one experiment; rapid and easy transition from one fluid to another; constancy of temperature and pressure.

SOME CHEMICAL FEATURES OF THE DIAPHRAGM AND OTHER SKELETAL MUSCLES

By FREDERIC S. LEE

In 1912 the author and Guenther reported the results of an investigation of certain of the physical features of the diaphragm of the cat as compared with certain other skeletal muscles. It was found that the diaphragm possesses a greater power of survival after the death of the animal, a greater resistance to the action of curare, a greater working power, a greater resistance to the oncoming of death, and a greater tendency toward rhythmicity in contraction. The investigation has now been continued with the aid of E. L. Scott, W. P. Colvin, and others into some of the chemical features of the muscles employed. These include the diaphragm as a muscle standing in some respects apart from all other skeletal muscles, the extensor longus digitorum and the sartorius as representatives of the paler muscles, and the soleus as a representative of the deeper red muscles. Thus far attention has been confined to the glycogen content, the power to reduce oxyhaemoglobin, and the phosphorus and sulphur contents of the lipoid fraction of the various muscles. The results are expressed in the following table in comparative figures, that of the diaphragm being reckoned in each case as a unit:

	Diaphragm	Extensor	Sartorius	Soleus
Glycogen	1.00	0.723	0.528	0.486
Reducing time	1.00	1.057	1.608	4.295
Lipoid phosphorus	1.00	1.015	1.440	
Lipoid sulphur	1.00	1.408	1.890	

It is seen from this table that with all four items the order of the muscles is the same; namely, the diaphragm, the extensor, the sartorius, the soleus. The greater content in glycogen which the diaphragm possesses may perhaps be associated with the greater working power of that muscle. The power to reduce oxyhaemoglobin was studied by means of Bonnhoffer's method. The muscles were quickly dissected out after death, rubbed up with powdered glass, placed at once in blood solution, and covered by a layer of olive oil to exclude the air. The time was then noted at which in each the spectrum of oxyhaemoglobin gave place to that of reduced haemoglobin. The diaphragm is seen to seize upon sufficient oxygen to bring about reduction somewhat more quickly than either of the pale muscles and much more quickly than the red soleus. The quantity of the phosphorus content of the lipoid fraction, which may perhaps be interpreted as signifying lecithin, is least in the diaphragm, slightly greater in the extensor, and still greater in the sartorius. The determination of lipoid phosphorus has not yet been made in the soleus. Similar quantitative relations exist with the sulphur content of the lipoid fraction, the significance of which is unknown.

THE EFFECT OF PULSATION ON FILTRATION

By R. A. GESELL

A METHOD for filtering solutions under constant and pulsatile pressure was described.

Various solutions were filtered through various membranes, with and without stirring, and the rate and nature of the filtrate noted.

Without stirring, the rate of filtration during the periods of pulsatile pressure was greater than the rate during constant mean pressure. With stirring, the effect of pulsation on the rate of filtration was not as marked, but the enhancing effect of pulsation was noted.

With the methods employed for the detection of urea, sodium

chloride, albumin, and casein — pulsation apparently had no effect on the content of these substances in the filtrate. In three experiments, in which defibrinated blood was filtered through the dog's peritoneum, more globulin appeared in the filtrate during the periods of constant pressure than during the periods of pulsatile pressure.

THE RÔLE OF NASCENT OXYGEN IN PROTECTING THE BODY FROM SELF-DIGESTION

By W. E. BURGE

Ptyalin, rennin, pepsin, amylopsin, lipase, trypsin, and invertase are destroyed by nascent oxygen. The nascent oxygen was obtained by the decomposition of hydrogen peroxide by a piece of platinum gauze on which platinum black had been previously deposited by the passage of the current. The amount of nascent oxygen could be governed by the amount of hydrogen peroxide introduced into the enzyme solution in which the platinum gauze was immersed.

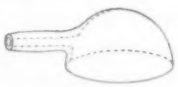
It was found that the amount of destruction of all these enzymes was more or less proportional to the amount of oxygen liberated in the solution and that all were destroyed by the amount of oxygen liberated from five cubic centimetres of hydrogen peroxide.

In the tissues, e.g., the stomach wall, there must be active or nascent oxygen because oxidation takes place there at a comparatively low temperature. From the above observations we know that pepsin is destroyed by nascent oxygen. A possible explanation of why the pepsin does not digest the stomach wall is that the active oxygen there oxidizes the pepsin which comes in contact with it. These observations also offer an explanation of why the diastatic enzymes in plants decrease during the day when nascent oxygen is being given off during the process of starch formation and why they increase in the dark when starch formation ceases.

CONVENIENT MODIFICATION FOR VENOUS PRESSURE DETERMINATIONS IN MAN

By D. R. HOOKER

The glass device shown is held in place over a superficial vein with a soft rubber band until the thin film of collodion placed in the angle formed with the skin has dried. The band is then removed. The pressure required to collapse the vein is recorded by the usual water manometer. The device is an improvement over other methods because it does not slip out of place or leak and because it is small and therefore facilitates, without much inconvenience to the subject, the making of observations during a number of hours. In the event of variations in the illumination of the vein becoming a disturbing factor it is sometimes useful to attach a small lever to the skin over the vein. When the vein is collapsed the lever point descends to an indicator level.



SALINE PERFUSION OF THE SPINAL CENTRES IN FROGS: THE EFFECT OF CALCIUM AND POTASSIUM CHLORIDE

By D. R. HOOKER and S. O. REESE

The decerebrate frog was opened and so far as possible all aortic branches ligated except those supplying the spinal cord. The triceps muscle was used to record reflex response, the stimulus (short tetani) for which was applied to the splanchnic fibres supplying the stomach. The irrigating fluid entered the bulbus and escaped from the great veins.

The effect of potassium is to increase uniformly the irritability of the reflex mechanism. Calcium produces the opposite effect. With the same stimulus, potassium reduces the latent period while calcium prolongs it. When, however, the stimulus bears a definite relationship to the degree of irritability the effect of calcium

seems to be to reduce the latent period below that obtained under the influence of potassium.

SOME PROBLEMS OF GROWTH

By THOMAS B. OSBORNE and LAFAYETTE B. MENDEL

(*a*) **The Capacity to Grow.** — The idea that the capacity to grow inevitably declines and is lost with age has obtained a firm foothold in physiological literature. We have tested the thesis by suppressing the growth of rats and mice for long periods — even far beyond the age at which it is ordinarily completed — without loss of the power subsequently to grow, in rate and extent comparable to what pertains in unchecked development. The retardation has been accomplished by various methods of inappropriate feeding, particularly with qualitatively inadequate proteins in the ration.

(*b*) **The Rôle of Amino-acids in Growth.** — On otherwise adequate diet which contained zein as the sole protein, rats declined rapidly in weight. A quantity of tryptophane equal to 3% of the zein added to the food maintained body weight; further addition of lysine (3%) caused a nearly normal rate of growth. When one-fourth of the zein was replaced by lactalbumin growth was normal. A like addition of casein or edestin induced almost no growth. Addition of tryptophane to the zein-casein diet or of lysine to the zein-edestin diet caused growth nearly equal to that made on the zein-lactalbumin diet. Addition of lysine to a food containing gliadin as its sole protein led to growth at a normal rate.

THE EFFECT OF VAGAL STIMULATION ON THE LOCATION OF THE PACE-MAKER IN THE MAMMALIAN HEART

By WALTER J. MEEK and J. A. E. EYSTER

In some fifty experiments we have verified the findings of Wybau and Lewis that the point of initial negativity in the

mammalian heart at the beginning of each cycle is in the sulcus terminalis immediately over the sino-auricular node.

During vagal stimulation irregular beats may arise from various parts of the heart. The origin of these has been studied by placing non-polarizable electrodes on the sinus node, the superior vena cava, the coronary sulcus as near as possible to the coronary sinus, the atrium of the right auricle, and the ventricular part of the auriculo-ventricular node. By special keys any two of these regions could be compared with each other by connecting them through the string galvanometer. In a series of over two hundred irregular beats appearing during vagal stimulation all but two were found to arise either in the sinus node itself or in some part of the auriculo-ventricular node. The two exceptions arose in the right auricle.

Atrio-ventricular rhythm was produced in twenty experiments by applying formalin, cutting around the sinus node, clamping the node and by stimulating the vagus. Primary negativity of some part of the auriculo-ventricular node was found to be the only absolutely constant criterion of these rhythms. In eight cases the part of the auriculo-ventricular node around the coronary sinus was found to be acting as pace-maker. A coronary sinus rhythm has thus been demonstrated.

Vagal stimulation itself not only occasionally caused atrio-ventricular rhythm, but in such rhythms it often restored the pacemaker to the sinus node provided this organ were only injured or partially isolated. In case the sinus node had been destroyed no other part of the heart could be made to supersede the atrio-ventricular node even on prolonged stimulation. In these cases, however, the pace-maker could be made to shift from the auricular to the ventricular part of the atrio-ventricular node.

With the aid of two galvanometers, one to compare the upper and lower portions of the sinus node and the other to serve as a control between the sinus node and the atrio-ventricular node, it was found that during vagal stimulation the point of impulse formation might pass downward to the lower end of the sinus node. This observation together with the shifting of initial negativity in the auriculo-ventricular node gives a physical basis

for explaining the gradual variations which appear in the As-Vs intervals as atrio-ventricular rhythm comes on.

Our work speaks strongly for the paramount importance of the specialized tissue of the intact mammalian heart in the matter of impulse formation. It also gives some experimental basis for the belief that vagal control is most marked on the most rhythmical part of the specialized tissue that is the upper part of the sinus node. When this is depressed some lower part less under vagal control acts as pace-maker. By increasing the strength of stimulation the whole heart may be finally stopped. On breaking through this inhibition the first beats, as would be expected, are often auriculo-ventricular in nature.

IMMEDIATE AND SUBSEQUENT EFFECTS OF ANAESTHESIA, LOW BLOOD PRESSURE, AND HANDLING OF THE INTESTINES UPON REFLEX CARDIO-INHIBITION

By HOLMES C. JACKSON and E. M. EWING

For the study of variations in irritability of the medullary centres, the reflex cardio-inhibition mechanism was chosen largely on account of the simplicity of its neural architecture and the directness of the muscular response. Examination of the *threshhold value* of this reflex under different conditions was undertaken rather than quantitative variations in responses, either absolute or percentile, as has been done in the case of the vasomotor reflex.

In most instances the results of reflex cardio-inhibition were compared with inhibition of respiration. The mechanism of the later reflex, as is also the case with the vasomotor reflex, is so complicated by unknown factors that the variation in responses may or may not bear a direct or parallel relationship to the acting stimulus.

The left vagus was cut and the central end stimulated with induced currents. Control experiments indicated that during

the course of four hours, the length of experimental procedure, the threshold value remained constant throughout. The threshold was examined under conditions of ether and of morphine anaesthesia, low blood pressure produced by hemorrhage and by partial and temporary ligation of the inferior vena cava, and trauma following severe handling of the intestines.

The following conclusions are warranted:

1. Ether raises and morphine lowers the threshold for this reflex.

2. Low blood pressure from hemorrhage. Pressures not below 60 mm. Hg and continuing for two hours do not alter the threshold; however, as the pressure becomes lower than this, the heart rate usually increases and the inhibitory reflex cannot then be elicited. That this is not entirely due to excessive cardio acceleration is indicated by the fact that where there is only a slight tendency towards increased heart rate, the threshold is also very high. Saline infusion tends to lower the threshold to an extent dependent upon the degree of the hemorrhage and the efficiency of the infusion in bringing the pressure back to normal.

3. Low blood pressure following ligation. Under these conditions the threshold becomes raised only when the pressure becomes as low as 25–40 mm. Hg. The heart rate is not so prone to increase and the threshold returns to normal more quickly upon raising the pressure than in the case of saline infusion following hemorrhage.

4. Dogs, whose pressure had been experimentally reduced by ligation to 40 mm. Hg and held there for two hours, recovered completely.

5. Severe handling of the intestines for two hours raises the threshold after a slight preliminary fall. Following the stoppage of handling, the threshold falls to the normal quite quickly. These statements hold when the pressure remains above 60 mm. Hg. If, following the handling, the circulatory regulation fails and the pressure falls below this figure, then the effects of low pressure influence the result.

OBSERVATIONS ON THE FORMATION OF CEREBROSPINAL FLUID

By F. C. BECHT

The present work was suggested by Dr. J. G. Wilson and is an attempt to secure evidence on the action of pilocarpine on the formation of cerebrospinal fluid, which has been used with good results in certain diseases of the labyrinth.

The method employed is to insert a cannula into the cisterna lying under the ligament extending between the atlas and the occipital bone, tie it into place, and record with a signal magnet the drops as they fall from the cannula. In many cases this method is inadequate and has been replaced by one used by Spina: The fluid is allowed to flow from the cannula into a glass tube with a bore of 1 mm. adjusted to the level of the cannula. The movements of the fluid are recorded in half centimetres from a metre stick upon which the glass tube is mounted.

The results secured do not warrant the belief that pilocarpine has any stimulating effect upon the structures forming the cerebrospinal fluid. It seems probable that the outflow results entirely from vascular changes within the rigid cranium.

The work is being extended to include other substances supposed to have specific effects upon the formation of cerebrospinal fluid.

FURTHER OBSERVATIONS ON THE METABOLISM OF DEPANCREATIZED DOGS

By JOHN R. MURLIN and B. KRAMER

Several experiments intended to ascertain the effects of hydroxyl ions on the output of sugar in the urine were reported. NaOH and Na_2HPO_4 increased the output of sugar per hour and $Ca(OH)_2$ decreased it. Simultaneous effects on the volume of urine indicate, also, that the influence of sodium on the kidney is to increase its permeability and the influence of calcium is to decrease it. This is in agreement with the report of Underhill and Classon.[1]

[1] Underhill and Classon: This journal, 1906, xv, p. 321.

The following experiment was cited as supporting the authors' previously reported negative effects of pancreatic extract on the respiratory metabolism of a depancreatized dog.

June 16	pancreatectomy	
June 19	5.52–6.52 P.M.	R.Q. 0.68
	6.52–7.52	R.Q. 0.71
	8.10 25 gr.	Dextrose by mouth
	9.55–10.55	R.Q. 0.74
	10.55–11.35	R.Q. 0.74

This indicates, possibly, a slight residual capacity to oxidize sugar.

June 20	3.22–4.22 P.M.	R.Q. 0.67
	4.22–5.22	R.Q. 0.69
	5.50–6.45 infused 350 c.c. Ringer's solution containing 1% Na_2CO_3	

During this time an extract of 3 pancreases in Henderson's phosphate mixture was infused by vein.

9.02–10.02	R.Q. 0.75
10.02–11.02	R.Q. 0.78
11.02–12.02	R.Q. 0.72

The increase in R.Q. could be more than accounted for by the Na_2CO_3 (3.5 gr.) administered.

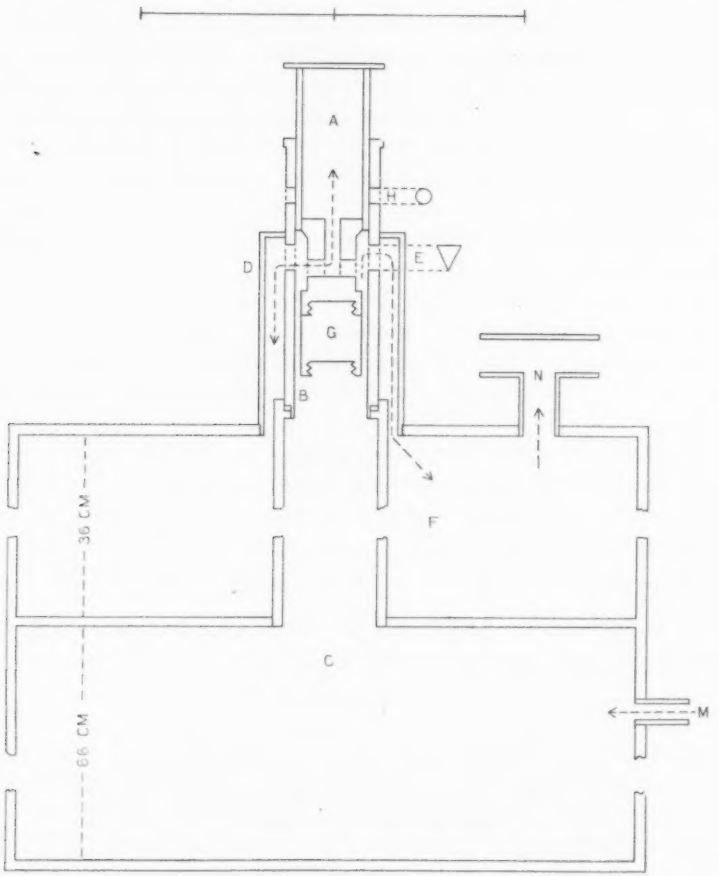
DEVICE FOR INTERRUPTING A CONTINUOUS BLAST OF AIR, DESIGNED ESPECIALLY FOR ARTIFICIAL RESPIRATION

By ROBERT A. GESELL and JOSEPH ERLANGER

In planning this apparatus our object has been to make use of compressed air in laboratories supplied therewith, for the purpose of giving artificial respiration by either the usual or the insufflation method, and in such a way as to render unnecessary the use

of any motive power other than that supplied by the compressed air itself for the purpose of interrupting the blast.

The apparatus consists of the double tank *C* (capacity 10,000



c.c. or more) *F* (capacity 6,000 c.c. or more) and the piston interrupter *G–A*. The air enters *C* through a cock at *M* and, when the piston *A* is down, passes through the pipe *B* alongside the weight *G* into the hollow piston *A*. At a pressure that is determined by the adjustable weight *G*, which is suspended verti-

cally under the point of support of *A*, the piston *A* is raised and so uncovers the paired triangular openings *D–E*. The air then escapes in the direction of the arrows into *F*, whereupon the piston *A* immediately falls back upon its seat closing the orifices *D* and *E*. The tank *F* acts as a buffer to take up the shock due to the sudden entrance of air into it and delivers the air through one of the outlets of *N*, which may be narrowed to further reduce the shock and prolong the escape of air from *F* into the tracheal cannula or catheter. The rate of interruption and the volume and pressure of the air delivered per interruption can be regulated within rather wide limits by adjusting the cock at *M* and the weight *G*. The openings at *H* serve as a safety valve. The piston *A* must fit snugly and work without friction.

EVIDENCES IN THE CEREBRAL CORTEX OF MENTAL EQUIPMENT AND INTELLECTUAL DEVELOPMENT

By E. LINDON MELLUS

As a supplement to results previously published, a report was made of the examination of the cortex of the third frontal convolution, in both hemispheres, of the brain of a former member of the American Physiological Society. This examination fully confirmed the results already reported and it appears probable that the brains of right-handed individuals will show that the cortex of an area surrounding the ascending anterior branch of the fissure of Sylvius is more highly developed on the left than on the right side. In these studies of Broca's area the most marked difference between the two sides is seen in the outer pyramidal and the granular, the second and third layers of Meynert. In these two layers of cells the depth is much greater on the left side, the excess varying from 10 to 60 and even 70 per cent. It is extremely difficult to determine just what has brought about this difference — whether the cells have been forced farther apart by the greater growth of processes and cell connections or whether it may not, in part at least, be due to an increase in the volume of the cells themselves, owing to a growth of the pro-

toplasm enveloping the nucleus. It seems possible that both these causes may contribute to the increase in depth.

Dr. Mellus believes the attempt of Campbell, Brodmann, and others to map out the cerebral cortex into a large number of areas on the strength of slight alleged differences in the type of cortex, representing fixed centres of various functions, is carried to an extreme altogether unwarranted. For one thing, they follow too closely the lines laid down in previous attempts at localization for entire freedom from bias.

In a further study of the brain above referred to, the cortex of the temporal lobe showed no marked differences in the two hemispheres. In comparison with the brains of three Austrian peasants studied in the same manner the cortex of the temporal lobes in the brain of the Professor was much less rich in cells; the cells were on the whole smaller and more scattered and the cortex thinner than that of the same areas in the brains of all three of the peasants. Those brains were from peasants who died in the General Hospital in Vienna and were studied in Prof. Obersteiner's Laboratory.

If we accept the view of those who would map out the cortex into areas of special function, we must look upon the auditory area as one of the most active functionally, at any rate during the early stages of education. In that case we would have to look upon the brain of the peasant as of one gifted naturally with possibilities far beyond those of the Professor. In that case our admiration for what the Professor had accomplished in the face of a heavy handicap would be accompanied by a sense of regret for what the world might have lost in the failure of another to make use of what had been given him.

TWO TYPES OF REFLEX REDUCTION OF BLOOD PRESSURE

By E. G. MARTIN and P. G. STILES

Stimulation of the central end of one vagus in the cat, the other vagus being cut, produces a depression of blood pressure

which varies in amount and in other features with the strength of the stimuli employed. If we note the strength of the shocks by the method of Martin (Z units) we find that when we begin with weak stimuli and increase there is a considerable range within which a small and transient drop of pressure results. This is often no greater when the stimulus is 100 Z than when it is 10 Z or even less. At a rather definite critical level a very much greater and more enduring effect upon pressure is produced. We believe that this level denotes the threshold of the "depressor mechanism" which is thus many times higher than the threshold for the reaction of the mild type. For example, it is a common experience to see a fall of only 6–8% in response to a stimulus rated as 100 or 150 Z and a fall of 25–30% following a stimulus of 200 Z. When this strong effect has been secured little or no additional lowering of pressure can be induced by the most radical intensifying of the stimulation.

THE METABOLIC GRADIENT IN THE NERVE FIBRE

By SHIRO TASHIRO

The different degrees of staining power, of susceptibility to drugs, and of electrical excitability along a nerve fibre strongly suggest the probable existence of different degrees of metabolic activity in the nerve. It was found that there is invariably a metabolic gradient in all nerves, if perfectly uniform fibres are selected. If the claw nerve (mostly efferent) of the spider crab is cut in two, the central portion gives twice as much carbon dioxide production as the peripheral portion. In the case of the afferent, optic nerve of the limulus, an opposite result is obtained, namely, the central portion (near the brain) shows decidely less carbon dioxide production than the peripheral portion. Whether this is due to parallelism between the direction of the normal conduction and the gradient of chemical activity in the nerve fibre, or to a simple embryonic relation between the axis cylinder and the nerve cell (for I have unfortunately chosen the optic

nerve) is not yet decided. The study of some sensory dendrites, now nearly completed, will decide this question.

Whatever may be its correct interpretation, the fact that there is a well-defined metabolic gradient in the nerve fibre may aid in the understanding of some electrical phenomena and of the general nature of nerve impulses.

THE ACTION OF ANAESTHETICS ON CARBON DIOXIDE PRODUCTION IN THE NERVE FIBRE

By SHIRO TASHIRO and H. S. ADAMS

With the view of gaining further evidence of the chemical basis of irritability, the action of various concentrations of anaesthetics upon carbon dioxide production from the claw nerve of the spider crab was investigated. We found that the lower concentrations (1% ethyl urethane and .4% chloral hydrate in sea water) which primarily stimulate the nerve, nearly double the carbon dioxide production of the resting nerve. On the contrary, higher concentrations (4% ethyl urethane and 2% chloral hydrate) which completely anaesthetize the nerve in ten minutes, but restore its excitability, considerably diminish carbon dioxide production of the resting nerve. Similar results are found in the case of the sciatic nerve of the frog and fertilized fish eggs, but quantitative results are not yet quite complete.

SOME PHYSIOLOGICAL FACTORS AFFECTING THE SPEED OF COAGULATION OF THE BLOOD

By W. B. CANNON and W. L. MENDENHALL

Stimulation of the splanchnic nerves is followed by a shorter coagulation time of the blood, which may change from approximately five minutes to approximately two minutes, and may continue at this low level for half an hour. Stimulation of the sciatic

nerve or operation under light anaesthesia has the same result. Excitement, either natural or induced by ether, is accompanied by rapid clotting, but this effect disappears if the splanchnics are severed. If the left adrenal gland is removed, stimulation of the left splanchnic nerve produces either no change or a prolongation of the clotting time; stimulation of the right splanchnic nerve still hastens coagulation. Small doses of adrenalin (.002 mg. per kilo), given intravenously, shorten coagulation. Larger doses (0.05 mg. per kilo) retard coagulation. The small doses have no effect if the circulation is wholly anterior to the diaphragm.